EXHIBIT D

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION THIS DOCUMENT RELATES TO ALL WAVE 1 CASES	Master File No. 2:12-MD-02327 JOSEPH R. GOODWIN U.S. DISTRICT JUDGE

<u>**EXPERT REPORT OF DR. VLADIMIR IAKOVLEV**</u>

Typographical errors corrected November 09, 2017, list of corrections attached on the last page.

I. BACKGROUND

I am an anatomical pathologist and director of Cytopathology at the Department of Laboratory Medicine, St. Michael's Hospital, Toronto, Canada. I hold an appointment at the Department of Laboratory Medicine and Pathobiology, University of Toronto. My professional activities include diagnostic examination of specimens surgically removed from human patients. These are larger excisions, smaller biopsies and cellular aspirations or smears. The organs and sites include genitourinary organs, gastrointestinal, head & neck, pulmonary, soft tissue and bone. My annual practice volume amounts to 3000-5000 cases. As a clinical physician, I provide clinical consultations to physicians at St. Michael's Hospital, which requires me to examine pathology specimens, review clinical information relating to the patient, and reach conclusions about the cause of a patient's injuries or illnesses. As an academic physician, I pursue research endeavors and teach medical students and residents. My academic activities also include tumor boards and teaching at CME workshops. I am also knowledgeable in the areas of chemistry, hematology, microbiology, serology, immunology and other special laboratory studies as they relate to my practice of pathology.

My pathology training was completed at the University of Manitoba Anatomical Pathology residency program, Canada. I hold medical licenses in the province of Ontario, Canada and in the State of Michigan, USA. As a pathologist with a subspecialty in anatomical pathology, I am a fellow of the Royal College of Physicians of Canada and a diplomate of the American Board of Pathology. For research training, I completed the Molecular Oncologic Fellowship Program at the Ontario

Cancer Institute, Toronto, Canada. A more complete description of my professional qualifications is set forth in my *Curriculum* Vitae, attached hereto. My research career started with a focus on the assessment of histological structures and biomarkers in tissues. Specifically, I became interested in accuracy of measurements, 3-dimensional distributions and tissue heterogeneity.

In 2012, I was approached by Dr. R. Bendavid, who is a recognized authority and an author of several books and numerous publications in hernia repair. He introduced me to the problems of mesh hernia repair, which, in comparison with non-mesh repair introduced unique complications of the mesh: chronic pain, migration and chronic infection. However the exact mechanism of these complications have not been fully studied. Previous studies and manufacturers' testing have been concentrated on experimental modelling in animals and controlled testing in a laboratory environment. A smaller number of research publications showed some pathological mechanisms in samples from patients.

As an anatomical pathologist at St. Michaels, I have reviewed over 250 cases of explanted meshes, including approximately 170 transvaginal mesh specimens. The specimens were from St. Michael's and referring hospitals as well as sent to me as a litigation consultant. All of the pathology that I have reviewed, regardless of the source, has been examined by me in the same manner that I would analyze routine diagnostic specimens according to the standard operating procedures of an accredited diagnostic laboratory.

Data collected from the assessed case have been reported in peer-reviewed journals and presented at scientific meetings as follows:

Full articles:

1. Bendavid R, Lou W, Grischkan D, Koch A, Petersen K, Morrison J, **Iakovlev V**. A mechanism of mesh-related post-herniorrhaphy neuralgia. Hernia. 2015 Nov 23. [Epub ahead of print]

2. V. **V. Iakovlev**, S. A. Guelcher, R. Bendavid. In vivo degradation of polypropylene: microscopic analysis of meshes explanted from patients. Journal of Biomedical Materials Research part B: Applied Biomaterials 2015; advanced online publication ahead of print.

3. J. G. Blaivas, R. S. Purohit, M. S. Benedon, G. Mekel, M. Stern, M. Billah, K. Olugbade, R. Bendavid, **V. Iakovlev**. Safety considerations for synthetic sling surgery. Nature Reviews Urology; August 2015, advanced online publication ahead of print.

4. **V. Iakovlev**, E. Carey, J, Steege. Pathology of Explanted Transvaginal Meshes. International Journal of Medical, Health, Pharmaceutical and Biomedical Engineering, 2014, 8(9): 510-13.

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5. Bendavid, R., Lou, W., Koch, A., Iakovlev**, V**. Mesh-Related SIN Syndrome. A Surreptitious Irreversible Neuralgia and Its Morphologic Background in the Etiology of Post-Herniorrhaphy Pain. International Journal of Clinical Medicine, 2014, 5:799-810

Abstracts:

1. M Thompson, D R. Ostergard, E Carey, S Guelcher, **V Iakovlev**. Court is in Session: Will Transvaginal Mesh Win or Lose? Interactive Seminar. International Urogynecological Association (IUGA), 40th annual meeting. 2015. Programme.

2. V. **V. Iakovlev**, S. A. Guelcher, R. Bendavid. Histological Features and Clinical Implications of Polypropylene Degradation. Canadian Journal of Surgery. 2015, 58(4 s2):46.

3. **V. Iakovlev**, A. Koch, R. Bendavid. Migration of Polypropylene Mesh in the Development of Late Complications. Canadian Journal of Surgery. 2015, 58(4 s2):46.

4. **V. Iakovlev**, G. Iakovleva, R. Bendavid. Systematic Pathological Assessment of Explanted Hernia Meshes Reveals Important Information of Mesh-body Interactions. Hernia. 2015;19 (S1) P5:04.

5. **V. Iakovlev**, G. Iakovleva, R. Bendavid.
Explanted Surgical Meshes: What Pathologists are Missing? Modern Pathology. 2015;28(S2):19A:63.

6. **Iakovlev V**, Mekel G, Blaivas J.
Pathological Findings of Transvaginal Polypropylene Slings explanted for Late Complications: Mesh is Not Inert. International Continence Society (ICS) annual meeting, 2014: 228.

7. R. F. Dunn, S. A. Guelcher, **V. Iakovlev.**
Failure Analysis of Transvaginal Mesh Products – a Biomaterials Perspective Using Materials Science Fundamentals. 2014 AIChE Annual Meeting: 112f

8. **V. Iakovlev**.
Explanted Surgical Meshes: What Pathologists and Industry Failed to do for 50 Years. Virchows Archiv 2014, 463(1): 337

9. **V. Iakovlev**, S. Guelcher, R. Bendavid.
In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked for Decades. Virchows Archiv 2014, 463(1): 35

10. **V. V. Iakovlev**, E. T. Carey, G. Iakovleva, J. Steege, R. Bendavid
Pathological findings associated with pain in transvaginal meshes. The 20th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI), 2014.

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Lectures and oral presentations:

1. What do we know about meshes in human bodies? Bard Davol European Hernia Symposium 2015. Berlin, Germany.

2. Migration of Polypropylene Mesh in the Development of Late Complications. Canadian Hernia Society meeting, 2015, Quebec city, Canada.

3. Histological Features and Clinical Implications of Polypropylene Degradation. Canadian Hernia Society meeting, 2015, Quebec city, Canada.

4. Court is in Session: Will Transvaginal Mesh Win or Lose? Interactive Seminar. International Urogynecological Association (IUGA), 40th annual meeting. Nice, France

5. Systematic Pathological Assessment of Explanted Hernia Meshes Reveals Important Information of Mesh-body Interactions. 1st World Conference on Abdominal Wall Hernia Surgery. 2015 Milan, Italy.

6. Pathological findings associated with pain in transvaginal meshes. The 20th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI), 2014 Paris, France

7. "SIN syndrome" – A New Mechanism for Mesh Inguinodynia. 1st Annual Abdominal Wall Hernia Conference, Canadian Hernia Society, 2014 Toronto, Canada.

8. Pathology of Explanted Transvaginal Meshes. International Conference on Obstetrics and Gynecology. World Academy of Science, Engineering and Technology. 2014, London, UK.

9. SIN syndrome: Pathological Findings in Explanted Mesh Specimens. Canadian Association of General Surgeons meeting (Canadian Surgery Forum), 2014 Vancouver, Canada.

10. In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked for Decades. 26th European Congress of Pathology, 2014, London, UK

11. Pathological findings in explanted surgical meshes. Shouldice Hospital, 2013, Richmond Hill, Canada.

Poster presentations:

1. Explanted Surgical Meshes: What Pathologists Are Missing? United States and Canadian Academy of Pathology (USCAP), annual meeting, 2015. Boston, United States

2. Pathological Findings of Transvaginal Polypropylene Slings. R. Ross research day, St. Michael's Hospital, 2014, Toronto, Canada.

3. Pathological Findings of Transvaginal Polypropylene Slings explanted for Late Complications: Mesh is Not Inert. International Continence Society (ICS) annual meeting, 2014, Rio de Janeiro, Brazil.

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4. Mesh-Related SIN Syndrome. A Surreptitious Irreversible Neuralgia and Its Morphologic Background in the Etiology of Post-Herniorrhaphy Pain. Canadian Association of General Surgeons meeting (Canadian Surgery Forum), 2014 Vancouver, Canada.

5. Explanted Surgical Meshes: What Pathologists and Industry Failed to do for 50 Years. 26th European Congress of Pathology, 2014, London, UK

For the opinions and figures in this report, I have relied on my findings in the explant specimens, including those transvaginal mesh devices manufactured by Ethicon. In addition, I have also relied on data available in peer reviewed publications, including my own peer reviewed publications. A short review of the published literature is provided below:

II.   LITERATURE REVIEW

Inflammatory reaction

Inflammatory reaction to the mesh is a non-specific reaction to a foreign body, which was initially described in the 1800`s during the time of Langhans and Metchnikoff [293] [347]. Immediately after placement into the body, foreign objects become coated with human proteins before appearance of the inflammatory cells. The inflammatory cells migrate into the tissue from the bloodstream through the action of inflammatory mediators. As in any tissue injury, short-lived neutrophils appear first at the site marking an acute phase. Neutrophils are replaced within days by macrophages, which stay in the area permanently. The phagocyte migration towards the foreign bodies is mainly dependent on the proteins coating the objects. [484] Specifically, fibrinogen has been shown to play a key role. [483] The macrophages either stay single, taking on an epithelioid appearance, or they fuse to form multinucleated giant cells. The fusion occurs in the presence of certain cytokines [340], which is usually seen when a foreign object is too large to be phagocytosed by a single cell. The collections of epithelioid macrophages and giant cells are the hallmark of granulomatous inflammation, which was originally described as a feature of tuberculosis. [293] The macrophages are recruited in an attempt to destroy the foreign object and the cells secrete an array of substances such as bioactive lipids, hydrolytic enzymes, reactive oxygen metabolites, and mediators of fibroblast proliferation. [294] [24] The cells adhere to the surface of the foreign object, similar to osteoclasts resorbing bone, and their main function is degradation of the foreign material. In addition to macrophages, granulomatous reaction includes T- lymphocytes as well as a smaller proportion of B-lymphocytes and plasma

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cells. Each mesh filament becomes surrounded by granulomatous inflammation and the entire mesh structure remains chronically inflamed indefinitely or until the mesh is surgically removed. [25] [153] [244] [265] [557] There are three aspects of mesh induced-inflammation which lead to complications for the patient: chronic foreign body inflammation, excessive scarring as a result of chronic stimulation of fibrosis, and polypropylene degradation.

Mesh integration

Mesh integration into the tissue is the result of repair mechanisms. As in any wound repair, these mechanisms aim to restore continuity of the tissues. Mammalian connective tissue does not regenerate except at fetal stages. In adult mammals, regeneration of soft tissue may occur to a limited degree in some animals. [321] [101] [421] [289] Normally, the damaged tissue and void spaces are filled with fibrous tissue, or scar. This fibrous tissue is used by our body as a non-specific universal repair material or filler. If the wound edges are closely approximated, the amount of scar is minimal and is known as "first intention healing". If the defect is larger, it needs to be filled with granulation tissue first – a process known as "second intention repair". [289] In relation to mesh, the body needs to repair the tissue damaged during surgery as well as to fill the spaces within the mesh structure.

After surgery, the void spaces are filled with blood clot. The clot, with its fibrin matrix, is used as a scaffold for cell migration. Neutrophils appear first, followed by macrophages, and then fibroblasts migrating from the viable edges. [289] [421] Blood vessels at the defect edges become a source of new sprouting capillaries formed by the proliferating endothelial cells. The capillaries supply nutrients for fibroblasts to synthesize collagen - the main component of future fibrous tissue. The initial loose collagenous matrix with abundant capillaries forms granulation tissue, which advances into the tissue defects and replaces the original blood clot and debris. In cases of implanted mesh, granulation tissue inhabits the spaces within the mesh structure – pores and interstices between mesh filaments. Over a course of weeks, the amount of deposited collagen grows, while fibroblasts acquire contractile filaments and transform into myofibroblasts. Their contractile function, together with reduction of extracellular fluid and collagen cross-linking, result in wound contraction aiming to minimize the volume of maturing scar. After the mesh is implanted in a body, the scar contracts within and around the mesh causing the fibers in the mesh to move closer to each other as well as to distort the physical

structure of the mesh. This leads to contraction, or shrinking of the composite mesh-scar structure. [263] [330] [162] [557]

Generally, in wound repair, axons of interrupted nerve branches grow to re-innervate their targets. [416] The same process occurs during tissue repair within and around implanted materials. Meshes implanted in either the anterior abdominal wall or transvaginally become innervated. [215] [216] [557] As anywhere in the body an innervated tissue is subject to all regular mechanisms of pain. The complicating factor in the meshes is tissue division into compartments. Each mesh pore or mesh fold is restricted by the mesh fibers. This tissue compartments include ingrown blood vessels and nerve branches. [215 [216] [557]

The next step in the repair process is maturation of the newly generated fibrous tissue. During this stage, collagen becomes more organized, and the density of microvasculature recedes. Initially, deposited collagen type III is replaced by collagen type I, rearranged to be parallel to tension forces, and cross-linked. The repaired area becomes hypocellular scar, which then is slowly remodeled for a year or longer. If there is repeated or continuous damage to the tissue, the process of repair can renew at any stage. Chronic conditions can generate a large amount of scar tissue due to the recurrent or continuous nature of the process.

In cases of foreign bodies implanted in the tissue, the repair process is complicated by the inflammatory reaction, which is a stimulus for fibrosis. The amount of scar tissue becomes dependent on the counterbalancing processes: stimulus due to foreign body and reduction of scar volume by remodeling. In relation to implanted meshes, fibrous tissue fills the spaces within the mesh structure and surrounds the mesh. [265] [273] [56] [215] [216] [557] Then, while the tissue undergoes contraction and remodelling, the stimulus for fibrosis is stronger around the mesh filaments and weaker away from the filaments, in the mesh pores. Some larger pores may include fat or other components of normal connective tissue, while the surrounding filaments are fully encapsulated by the scar. [274] Where the scar spans, or bridges across the pores, it is termed bridging fibrosis. Mesh designs containing pores of several millimeters (lightweight) after accounting for stretching forces (either during implantation or in vivo), have a greater chance to contain normal non-scar connective tissue. [274] [273] However, the mesh designs that are currently used for transvaginal devices, including the Prolift line of products and the TVT line of products, show a continuous scar plate that encases all of the mesh filaments and spans

across nearly all of the pores.   [274] [183] It also provides a rigid connection between the composite mesh-scar structure and the surrounding normal tissue.

Polypropylene degradation

For nearly a half century, scientists around the world have studied polypropylene, including Ethicon's Prolene used in TVT product and have consistently found that polypropylene degrades over time after being implanted in the body. [386] [229] [110] [102] [112] [529] [337] [271] [467] [247] [431] [448] [64] [310] [556].

For example, dating back to the 1970s, Liebert *et al.* found that polypropylene will degrade *in vivo* over time if not adequately protected by antioxidants. [310] In 1998, Prolene was compared to another polymer called PVDF in an animal study.[337] The researchers found that explanted Prolene degraded after 1 and 2 years, while PVDF remained intact. Similarly, later studies also found that surgical polypropylene mesh will degrade over time after implantation in the human body.[110][102][529] [556] Environmental stress and oxidative degradation facilitated by macrophages have been found to be the most likely mechanisms to explain *in vivo* degradation of polypropylene. [60] [337] [386] [229] [110] [102] [112] [529] [337] [271] [467] [247] [431] [448] [64] [310] [556].

Recently, degradation of polypropylene was detected using histological and transmission electron microscopy approaches [211] [215] [216] [556]. This was observed using a combination of histological stains in regular and polarized light. Polarized light microscopy has been reliably used for nearly 100 years to describe the characteristics of explanted foreign materials. [470] As demonstrated by Ethicon's internal documents, the histological methods have been used by Ethicon's scientists to determine whether Prolene degrades in vivo. The findings lead Ethicon's scientists to conclude that Prolene degrades forming an outer layer of degraded material and the cracking observed on the surface of Prolene by scanning electron microscopy is altered polypropylene and not proteinaceous material. [156] The main feature of degradation is cracking of the polypropylene surface [386] [229] [110] [102] [112] [529] [556]. Similar process occurs outside the body. [467] [247] [431] As a result, the material loses tensile strength and becomes brittle. Loss of mechanical properties was shown in explanted meshes. [448] Cracking also indicates that there are internal forces acting to shrink and deform the material. In relation to clinical symptoms, degradation needs to be considered as a factor of additional stiffening and late deformations of the mesh, independent of stiffening and deformations related to scar

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maturation, ingrown scar contraction, mesh folding/multilayering.   An important conclusion should be made that if chemical and physical properties of a material change while it is in the body it should not be used for permanent applications and for anatomical sites from which the devices cannot be safely removed. There should be planned exit strategies for complete and safe device removal and with minimal residual tissue damage.

The literature also includes a much smaller number of publications that question whether polypropylene fibers degrade in vivo. [467] [247] [558]   The alternative hypotheses were that the cracking either occurs within a proteinaceous layer (i.e., biologic) or was caused by sample preparation (e.g., drying, formalin or chemical reagents used to clean the explanted material prior to examination). Ethicon's experts have similarly espoused in prior cases that a protein-formaldehyde polymer forms around the mesh fibers while the mesh is being stored in formalin. The hypothesis has not been proven and Ethicon's own scientists made conclusions disproving this hypothesis. The hypothesis is not viable since there are multiple features disproving it: the degradation layer retains premanufactured dye granules and optical properties of polypropylene, is can melt and meld with non-degraded polypropylene, cracking of the mesh fibers can be observed immediately after the mesh is removed from the body, the degradation layer does not form around some other implantable materials (GoreTex, polyester), its thickness correlates with time in the body but not with time of storage.[556] Also, testing of polypropylene by multiple manufacturers indicates that it is resistant to formalin, which contradicts the theories that exposure to formalin causes polypropylene to degrade. [555]

Review of Ethicon's internal documents

In addition to my review of the peer-reviewed publications, I have also reviewed internal Ethicon documents and the deposition of an Ethicon scientist, Dr. Thomas Barbolt. Ethicon's internal documents and the testimony of Dr. Barbolt provide further evidence that the Prolene will degrade over time after implantation in the human body.

In 1983, Ethicon's scientists used nearly identical methods used by me to determine whether Prolene degrades *in vivo*, including histological preparations, light microscopy, and polarized light. [156] Like my own studies discussed herein, Ethicon's scientists found that Prolene degrades and cracks after implantation in the human body. Interestingly, just as I found in this and other mesh explants, Ethicon's scientists opined that "the cracked layer appeared blue in gross specimens and blue dye particles were evident in histological sections of the layer. This

would indicate that the layer is dyed Prolene polymer and not an isolated protein coating on the strands."[156] Thus, using nearly the same methods as I use routinely in my practice as a pathologist, including the work I performed in the present cases, Ethicon's scientists concluded not only that the surface of Prolene degrades *in vivo*, but also that proteinaceous material was not a likely cause to explain the surface cracking observed on the explanted Prolene fibers, undermining the hypothesis that the cracked layer observed on explanted Prolene fibers is biological or proteinaceous in nature rather than degraded polypropylene.

Ethicon's scientists continued to study *in vivo* changes of Prolene and their findings were consistent throughout the years. For example, Ethicon conducted a 10-year dog study that began in 1985. During the 10-year dog study, Ethicon's scientists concluded "the PROLENE surface, intact at the two year point, showed signs of degradation at five years."[157] Ethicon's scientists also determined that sample preparation was not what caused the cracking: "it can be said unequivocally that the cracking that was seen in any of the sutures was not introduced by sample preparation, i.e., drying. If cracking was observed on a dry suture in the light microscope or in the SEM, the same cracking was also found on the same suture after it had been in body fluids and then in sterile water, without ever having dried."[157] Moreover, formaldehyde was not used in this dog study, further undermining any claim that the cracking observed on the explanted Prolift and/or TVT devices is caused by a formaldehyde protein polymer.

After seven years, Ethicon's scientists reached a similar conclusion made years later by Mary *et al.*, that "degradation in PROLENE is still increasing and PVDF, even though a few cracks were found, is still by far the most surface resistant in-house made suture in terms of cracking."[158]

Furthermore, in 1987, Ethicon's scientists conducted a number of studies using human Prolene explants provided by Prof. R. Guidoin and likewise concluded that the Prolene degraded *in vivo*.[132] [159]

I also reviewed the deposition of Ethicon's scientist, Dr. Thomas Barbolt, who testified that the antioxidants used by Ethicon to protect Prolene from degradation can leach out of the fibers into the host tissue. [133] Dr. Barbolt testified that the Prolene used to manufacture both the Prolift products and the TVT products can undergo surface degradation. Dr. Barbolt further testified that Prolene can undergo surface degradation and that it was known by Ethicon before 1992, and that it was falsely stated in the IFU that Prolene is not subject to degradation. [133]

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Effect on the tissue

Pain

Scar tissue inhabiting the mesh is not inanimate filler, but living tissue with vasculature, innervation, fluid and acid-base balance, and immune response. [56] [388] [464] [557] The tissue is subject to regular mechanisms of pain, out of which there are two main mechanisms for pain: direct irritation of nerve branches and irritation of receptors they supply.

Direct irritation of nerve branches can occur due to nerve entrapment with scar tissue within or encapsulating the mesh. [56] [216] [266] [274] [351] [509] [557] The nerves can also become distorted while growing through the mesh and can form traumatic neuroma, a tumor like nerve enlargements known for its painful nature. [274] [351] [509] The entrapped and distorted nerves are also at risk for additional pulling, compression and distortion forces due to the earlier described mesh-scar contraction and non-physiological attachments to the surrounding mobile tissues. Nerve involvement has been reported to exceed 60% for meshes excised for reasons of pain. [274] [56]

In regards to irritation of pain and other receptors the risks are due to specific factors: persistent chronic inflammation, fluid balance, blood supply, physical interlock within the mesh, and non-physiological attachments to mobile tissues. During our lifetime, we all experience the effect of inflammatory mediators causing hypersensitivity of pain and other (touch etc.) receptor. This leads to pain to touch or with movement, and if a stimulus is sufficiently high, it can cause pain at rest. [249] As discussed earlier, polypropylene meshes are invariably associated with a chronic inflammatory response, which creates the background capable to lower the pain sensitivity threshold.

Another specific factor within the mesh-scar complex is its compartmentalizing nature and attachments to the surrounding tissues. The ingrown tissue is in a vulnerable position for physical compression and distortion within the compartments of mesh pores and folds. The risk of compression can occur as a result of external forces, as well as from increased interstitial fluid pressure within the compartments. Externally, scar connection to the surrounding tissue leads to distortion and pulling during movements. Additionally, mesh shrinking during scar contraction leads to static tension within and between the attached tissues.

It is important to note that in hernia surgery, where chronic pain after mesh repair is a growing problem prophylactic neurectomy is offered as a method to reduce incidence of pain after mesh repair. [227]

Mesh migration

Mesh migration through the tissues and into the adjacent organs has been described in hernia applications, where two types of migration were suggested: primary migration of unsecured mesh towards least tissue resistance, and secondary migration through transanatomical planes. The latter is facilitated by tissue forces acting to displace mesh and by the environment making the movement possible: specifically tissue resorption facilitated by inflammation and the ability of tissue to remodel. [192] [10] In the case of transvaginal devices, the migration occurs into or through the urethral or bladder wall, [130] [65] [299] [76] which is a secondary type of migration. Mesh migration is also one of the mechanisms for mesh erosion through vaginal mucosa.

Deformation (folding, curling)

A related phenomenon is mesh deformation, where a part of mesh moves from its original or intended position. Comparatively, during the search for the "ideal mesh", knitted meshes were found to be more prone to fold or curl at the edges. [152] Similar to migration, deformation can be primary due to intra-/perioperative folding and edge curling of an unsecured mesh, or secondary occurring after tissue ingrowth. Secondary wrinkling, folding, curling or "roping" is attributed in large part to forces placed on the mesh both during implantation and in vivo as well as mesh-scar contraction. [263] [354] [389] [545] [546] [553] [557]

Contraction/Shrinkage

For many years, it has been widely reported in the scientific literature that polypropylene surgical meshes undergo what has been called "mesh contraction" or "mesh shrinkage" after implantation in the body's tissues. [274] [266] [547] [548] [549] [550] [551] [552] The mesh fibers themselves do not shrink; rather, it is the wound or damaged tissue surrounding the implant which undergoes normal wound contraction that causes a reduction in the surface area due to retraction of the fibrotic scar tissue in and around the mesh implant. All polypropylene meshes will contract in variable amounts, reportedly between 20 -50 % or more of the original surface area. The contraction tightens the mesh devices and leads to tissue and organ damage.

One of the clinical manifestations of mesh tightening by contraction is the mechanism for urinary outflow obstruction.

Mesh stiffening

Ethicon's IFU claims that the mesh will remain soft and pliable after implantation into the women's pelvis. Contrary to this claim, however, as a result of the excessive scaring around the mesh, as well as the *in vivo* degradation of the mesh the mesh devices become harder and more rigid after implantation than pristine devices. [523] [223] [263] [261] [227] Elasticity of pristine mesh is due to movements and bending of the mesh fibers. After implantation the mesh acts more like stiff rebar within the scar tissue while the ingrown scar blocks movement of the mesh fibers. Thus both the mesh and the scar act to stiffen and harden the composite mesh-scar structure. The resultant mesh-scar plate is stiffer and harder than the surrounding normal soft and elastic tissue. While the scar matures to stable firmness within a year, degradation of polypropylene with resultant stiffening of the mesh is progressive over the years. Therefore, the initial stiffness due to mesh folding/curling and scarring is further aggravated by material degradation over the following years in the body.

III.   OPINIONS

I hold all opinions set forth in this expert report to a reasonable degree of medical and scientific certainty. The basis for each of my opinions is my education; my training; my professional experience as a pathologist; and the published, peer-reviewed medical and scientific literature, including my own peer reviewed literature. Each of the opinions and figures identified below are based on my review of the Ethicon's transvaginal mesh specimens the specimens that have been reviewed and identified in published peer reviewed journals.

<u>Summary opinion</u>

The mesh acts as a foreign object and the body attempts to degrade and isolate the mesh. The mesh itself, as a foreign object, and the body reaction to the mesh damage the tissues in a critical anatomical location. This damage occurs in all patients, however to a variable degree. The manifestations range from subclinical to fully developed complications triggering mesh excision.

The components of the above opinion are as follows:

1. **Critical anatomical location.**

Synthetic implantable materials act as foreign bodies which can cause complications for all implantable devices, but this drawback becomes especially critical in the transvaginal locations due to the following factors:

- There are no sharply separated parallel anatomical planes, but rather several round mobile organs in a narrow pelvic space. The mesh cannot be placed parallel to the organs and is not separated from them by anatomical structures.

- There are several organs that need to expand and contract for their function. The mesh cannot contract or expand, moreover, together with encapsulating scar it provides non-physiological connections to the mobile organs.

- The devices are designed to be implanted superficially under sensitive mucosa and can easily become eroded through the mucosa, either due to mesh migration or mucosal breakdown.

- The devices are designed to correct anatomical position of the organs, therefore are designed to press against the organs. This pressure can force the mesh to migrate into the organs.

- Placement through contaminated field and mesh exposure provide routes for infection.

- The mesh devices cross paths of normal innervation and vascular supply to the mucosa, the bladder and the rectum. After implantation the innervation and vascular supply need to be restored either through or around the mesh.

- The arms and slings are designed to be pulled through the pelvic deep soft tissue and skin, therefore they cross muscles and innervation network of the soft tissues and skin.

2. **Foreign body type inflammation**. The mesh causes a foreign body response.   This reaction is aimed to degrade the foreign object and persists until the inciting agent is either removed (expelled) or resorbed (degraded).   The reaction is observable microscopically. Images in Figure set 1 are representative of the foreign body response to the Ethicon transvaginal mesh.

3. **Scar ingrowth and encapsulation.** After implantation, the empty spaces within the mesh have no pre-existent tissue and become filled by fibrous tissue, or scar. The surrounding normal tissue can be pulled into the spaces focally during scar contraction and

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maturation, but the filaments are always surrounded by fibrous scar. While scar formation is a physiological part of healing process, it is not a functional, but a non-specific replacement tissue. Scar formation is further exacerbated and amplified by the inflammatory stimulus described above. These processes result in a formation of a mesh-scar plate. The mesh and the scar tissue form a composite structure where both, the mesh and the scar reinforce each other and the composite structure is stiffer than a new mesh or scar tissue without the mesh within. Images in the Figure set 2 are representative of scar plate formation in a woman's pelvis as a result of the implantation of the Ethicon transvaginal mesh devices.

4. **Mesh contraction.** As any scar tissue, the scar within and around the mesh contracts during maturation. This leads to contraction of the mesh-scar composite structure. Contraction of the mesh results in its deformation and tightening. Overtightened devices can compress organs and tissues. Tightened devises also can form ridged bands under sensitive mucosa.

5. **Mesh-scar innervation.** The scar inhabiting and encapsulating the mesh is innervated where the nerve branches grow around the mesh and through the mesh pores to re-innervate their targets interrupted during surgery as well to innervate the new tissue (neo-innervate). The innervated tissue is exposed to all regular pain mechanisms of direct mechanical irritation of the nerves as well as irritation of the receptors by the inflammatory and physical mechanisms of pain. Since the compartments are fused by fibrous tissue, the 3-dimensional mesh structure becomes fixed and the neurovascular structures become trapped within. By contrast, mature scar tissue after non-mesh surgeries does not show inflammation, does not have compartmentalization of mesh structure, and can remodel with time, therefore does not exhibit the same risk for pain. Images in Figures set 3 are representative of Ethicon transvaginal mesh innervation in the pelvis.

6. **Severe deformation of nerves and formation of neuroma type lesions.** Traumatic neuromas are known to be painful lesions. Similarly, nerves can become damaged by the mesh, either by migration or during contraction. Severly distorted nerves form traumatic neuroma type lesions. Some nerves can show degenerative type lesions. Figure set 3.

7. **Involvement of neural ganglia.** The mesh can also affect neural ganglia indicating that innervation of the internal organs such as urinary bladder and the rectum can also become

affected. Microphotographs of mesh affecting the neural ganglia are shown in Figure set 4.

8. **Innervation of female genital organs.** Furthermore, the female genital area has much higher nerve density compared to the midline anterior abdominal wall and the groin. The scar inhabiting and surrounding the transvaginal meshes has the highest nerve density out of all explanted surgical meshes I have examined as a pathologist. Thus, placement of the vaginal mesh is associated with higher risk for chronic pain than the placement of the mesh for hernia repair, either ventral or in the groin.

9. **Stiff irregular mesh-scar plate under sensitive mucosa.** The hardened and stiffened mesh-scar plate is located under richly innervated and sensitive vaginal mucosa. This relationship puts the mucosa under risk for pain if it becomes compressed against the mesh-scar plate (intercourse, tampon use). Examples of mucosal innervation over the mesh are shown in Figure set 5.

10. **Higher sensitivity for pain due to inflammation.** As discussed earlier, the mesh is invariably associated with a chronic inflammatory response. It is known that inflammatory mediators lower sensitivity threshold of the pain and other receptors. Therefore tissues surrounding the mesh are more sensitive for pain than a scar without inflammation.

11. **Tissue edema.** It is well studied that inflammatory mediators can change vascular permeability and tone which leads to tissue swelling (edema). Edema can be also caused by partial constriction that is sufficient to compress the low-pressure outflow vessels (venules and lymphatics), but not the inflow arteries and arterioles. Thus pain due to swelling is present in cases of inflammation and trauma and the effect is amplified in rigid compartments. A knitted mesh introduces multiple compartments and constriction points as the mesh pores and folds/curls. There are areas with dilated and congested vessels and edematous stroma within the mesh pores and folds. Images in Figure set 6 are representative of these pathological changes in the female pelvis as a result of the Ethicon transvaginal mesh.

12. **Involvement of striated (skeletal) muscle.** In explanted Ethicon transvaginal mesh devices striated muscle has been detected either interpositioned through the mesh structure, connected to the mesh by the scar, or surrounding the mesh on both sides. Figure set 7 shows representative

examples of the presence of striated muscle in explanted mesh devices. In the cases when the muscle is attached to the mesh, muscle contraction can result in pulling of the entire mesh, the scar tissue, and the nerves that have ingrown into the scar. The resultant pain can irritate the muscle and cause a spasm type contraction as it occurs in renal and biliary colics or muscle spasm in the cases of back pain. This can cause a self-propagated pain-spasm reaction.

13. **Involvement of smooth muscle of the vaginal wall, urinary bladder, urethra and rectum.** In explanted transvaginal mesh devices, the smooth muscle of the pelvic organs can become affected by the mesh. Microphotographs in Figure set 8 are representative of the presence of smooth muscle in explanted mesh devices. This can interfere with the muscle contraction and the organ function and can also apply a force to the mesh during muscle contraction. Involvement of the muscle of the bladder and urethra can affect their function and produce sensation during muscle contraction. Connection to the smooth muscle of vaginal wall can interfere with its contraction (intercourse etc.). Mesh migration into the rectal muscle can be felt and interfere with bowel movement.

14. **Vascular thrombosis and obliteration.** Mesh placement is associated with vascular damage, where both the larger vessels and the smaller capillaries can become affected. Tissue affected by insufficient blood supply can undergo necrosis and/or fibrosis (scarring). Ischemia can also be associated with sensation of pain. Examples of vascular damage are shown in Figure set 9.

15. **Mesh folding and curling.** In addition to the mesh pores and interstices, a deforming mesh forms curls and folds that become partially enclosed compartments. These compartments provide a similar mechanism for ingrowth and entrapment of the nerves, vessels and the muscles identified above. Curled and folded mesh is stiffer than a single layer of a flat mesh. A curled/rolled sling tape also has a smaller area for pressure distribution and has a higher chance to cut through the tissues than a flat tape. Irregularly folded larger pelvic organ prolapse devices exercise focal pressure on the tissues at the prominent folds and form ridges and bands. Figure set 10 shows representative images of curling/folding of Ethicon mesh that has been explanted from the female pelvis.

16. **Mesh migration**. The mesh can migrate in the human tissue. The migration is either primary (intra/perioperative migration of unsecured mesh) or secondary (inflammation and tissue remodelling provide path for the mesh to migrate while body forces act to displace the mesh). Its migration causes damage of the tissues on its path: such as mucosa, nerves, vessels, neural ganglia, urethra, bladder and the rectum.

17. **Mucosal erosion**. Mucosal erosion of the mesh is a complication unique for the mesh surgeries. It cannot happen without the use of mesh. There are two main mechanisms for mesh erosion:

mesh migration and the breakdown of the overlying mucosa. Mesh migration is discussed in #15. The mucosal breakdown can have complex mechanisms where infection, vascular supply, tissue mobility, size and depth of the mesh device and other factors can play roles. Images of mucosal erosion are shown in Figure set 11.

18. **Acute inflammation due to mucosal erosion.** Mucosal erosion of the transvaginal Ethicon mesh becomes a chronic open wound and an entry for infectious organisms. This is associated with acute inflammation and formation of granulation tissue. Fragile granulation tissue produces discharge and bleeds easily. Presence of bacterial infection triggers acute inflammatory response which becomes superimposed on the earlier described chronic non-specific and foreign body type inflammation. Examples of superimposed acute inflammation are shown in Figure set 12. This additional inflammation plays role in tissue damage and further stimulus for pain receptors.

19. **Polypropylene degradation.** Microscopic examination of explanted Ethicon mesh confirms what has been reported otherwise in the medical and scientific literature: polypropylene degrades *in vivo*. Examination reveals a polypropylene degradation layer on the outermost layer of the mesh filaments. The layer differs from the non-degraded core by its ability to trap histological dyes in the nanocavities produced in polypropylene due to degradation. At the same time the degraded material retains inclusions (blue granules) and optical properties (birefringence in polarized light) of polypropylene. Figure set 13 shows representative images of the degradation layer in explanted Ethicon transvaginal mesh devices.

20. **Absence of degradation after exposure to formalin and chemicals of tissue processing.** Polypropylene of pristine polypropylene mesh, including Prolene does not degrade due to exposure to formalin. This has been shown in my experiments and testing by several manufacturers. Examples of mesh after exposure to formalin up to 4 month followed by routine tissue processing are shown in Figure set 14.

21. **Gradual growth of the degraded year over the years in the body.** The degraded layer on an implanted polypropylene mesh, including Prolene accumulates gradually over the years in the body. See Figure 15. As a result, the mechanical properties of the mesh fibers change. The degraded layer cracks indicating its brittleness. As in many brittle porous materials brittleness and porosity are not exclusive of each other.

22. **Cracking of degraded layer observed immediately after mesh removal from the body.** The cracked degradation layer can be visible immediately after excision See Figure

18

16. The claims that the cracked layer is dried biofilm-proteins or formalin-protein polymer are unsubstantiated since cracking can be seen before the proteins could dry or be cross-linked by formalin.

23. **Melting of degraded polypropylene due to surgical cautery.** The degraded layer shows sites of melting occurred during the use of surgical cautery during excision. This finding confirms that the degraded layer was present before the excision surgery and formed in the body. The bark mixes with the non-degraded core while melting which confirms that it is compatible with the core polypropylene. The feature is shown in Figure set 17.

24. **Absence of stainable layer on non-polypropylene implantable polymers**. In cases when polypropylene mesh was secured by non-polypropylene permanent sutures the non-polypropylene materials do not show formation of a stainable outer layer. If the layer was formed by body proteins it would not have a strict preference to one polymer. See Figure set 18.

25. **Correlation with internal Ethicon documents.** Based on the features described in opinions 16-23, review of the body of scientific literature, review of Ethicon's internal documents and internal studies, it is my opinion that Prolene polypropylene used by Ethicon degrades *in vivo*. Figure sets 19.

26. **Degenerative calcifications can form** triggered by the mesh related pathological tissue changes.The calcific deposits are different from degraded polypropylene. In cases were the mesh migrates into the bladder these calcifications can grow to larger bladder stone.

27. **Mesh excision cannot restore pre-existent tissue state.** Mesh placement causes tissue damage, then while in the body the mesh induces scarring, contracts and migrates expanding the zone of tissue damage. An excision either removes the mesh and all surrounding scarred/damaged tissue leaving a larger defect, or partially removes the scar plate leaving a smaller defect but with a larger amount of remaining scar. In either scenario the defect needs to heal through scarring. Additionally, in many cases mesh cannot be removed in its entirety, especially from the transobturator and other difficult to access locations.

I reserve the right to supplement this report if new information becomes available.

Sincerely,

Vladimir Iakovlev, MD, FRCPC, FCAP   DATE: January 29, 2016

 Typographical errors corrected October 17, 2017, list of corrections attached on the last page.

FEES

My billing rate is $475/hr.

**LISTING OF CASES IN WHICH TESTIMONY HAS BEEN
GIVEN IN THE LAST FOUR YEARS**

Lisa Marie Fontes, et al. v. American Medical Systems, Inc.; 2:12-CV-02472

Debbie Jilovec, et al., v. American Medical Systems, Inc.; 2:12-CV-05561

Joann Serrano, v. American Medical Systems, Inc.; 2:12-CV-3719

Mary Weiler, et al. v. American Medical Systems, Inc.; 2:12-CV-05836

Carolyn F. Smothers v. Boston Scientific Corp. ; 2:12-cv-08016

Katherine L. Hall v. Boston Scientific Corp. ; 2:12-cv-08186

Julia Wilson v. Boston Scientific Corp. ; 2012-02626

Ronda Orozco, et al., v. Boston Scientific Corp. ; 2012-03068

Maria Cardenas v. Boston Scientific Corp. ; 2012-02912

Diane Albright v. Boston Scientific Corp. ; 2012-00909

Deborah Barba v. Boston Scientific Corp.

FIGURE SETS

**All images represent explanted Ethicon transvaginal devices (unless indicated otherwise)
Estimated cropping magnifications are shown as approximate microscope objective.**
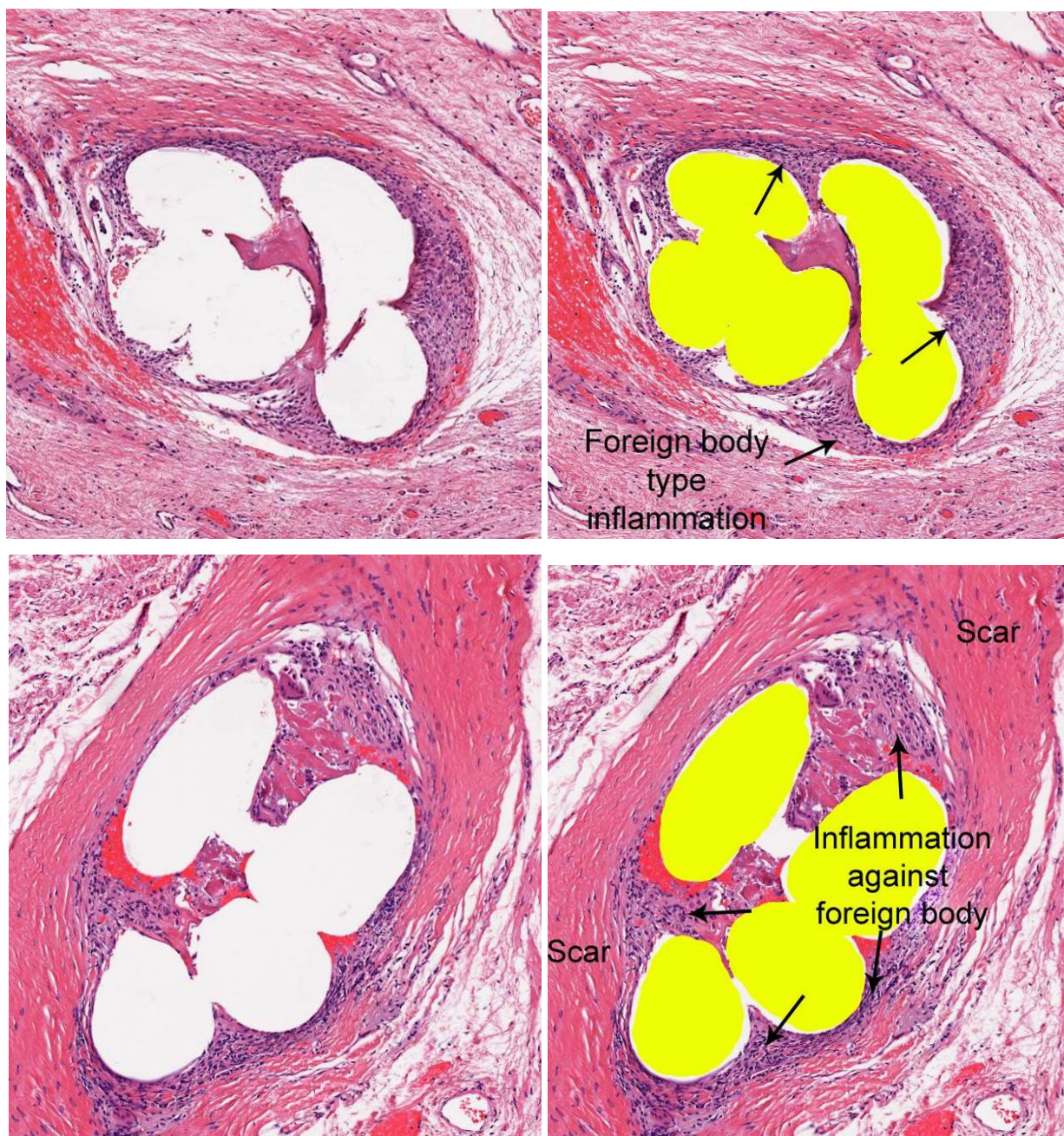
Figure set 1a. Foreign body type inflammatory reaction, H&E, 40x.

21
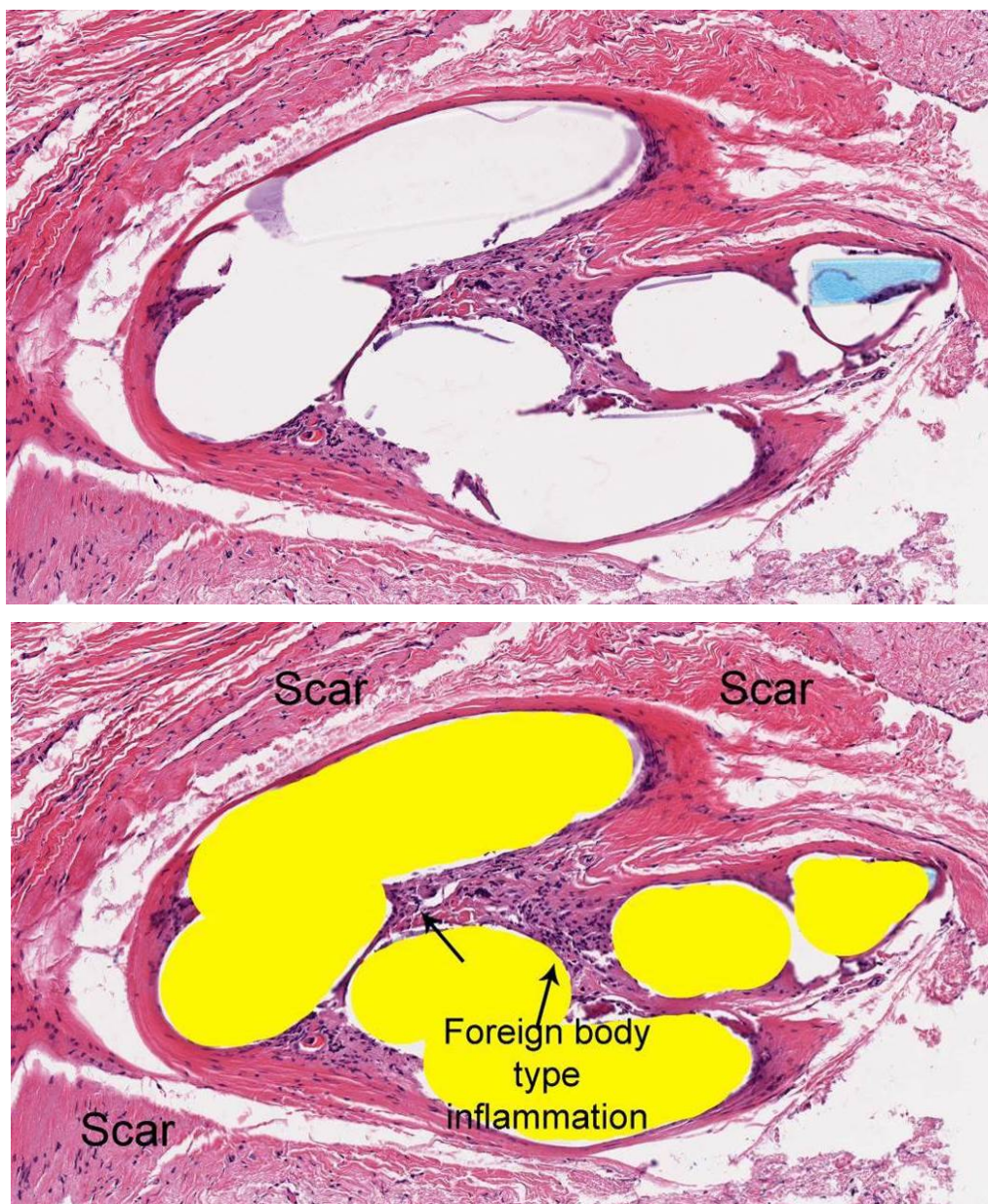
Figure set 1b. Foreign body type inflammatory reaction, H&E, 40x.

22
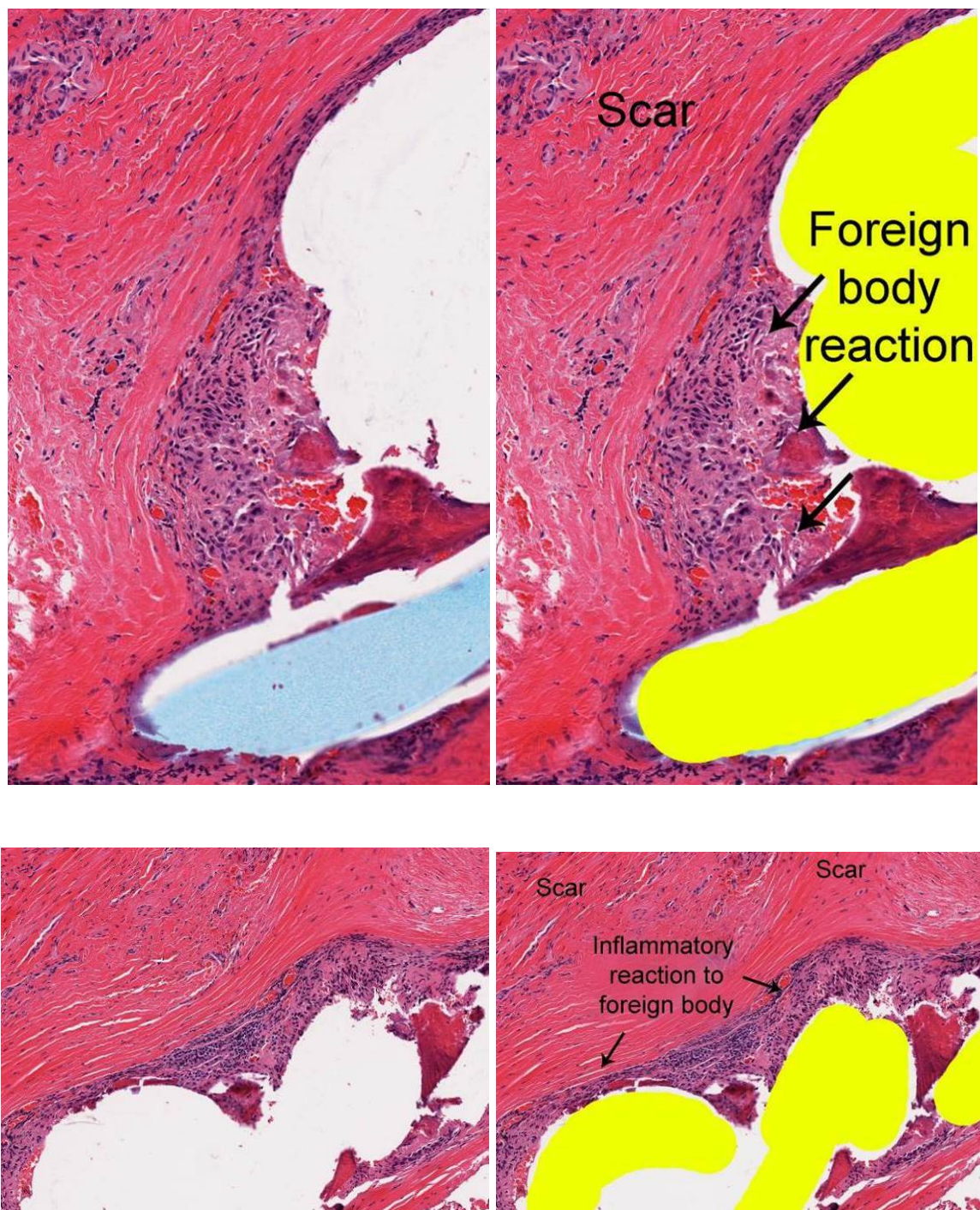
Figure set 1c. Foreign body type inflammatory reaction, H&E,40x.
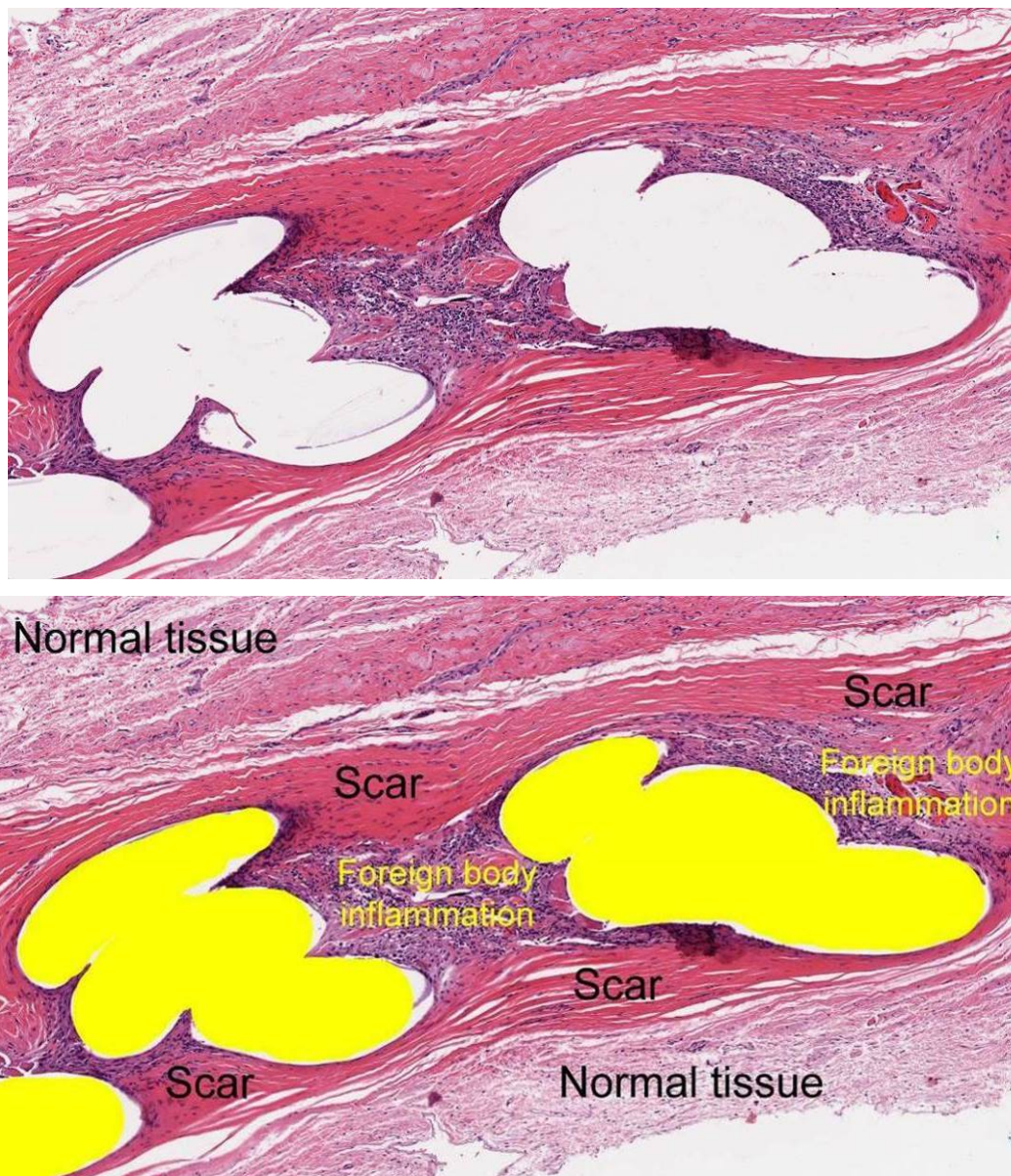
Figure set 2a. Fibrous bridging and scar encapsulation, H&E, 20x.
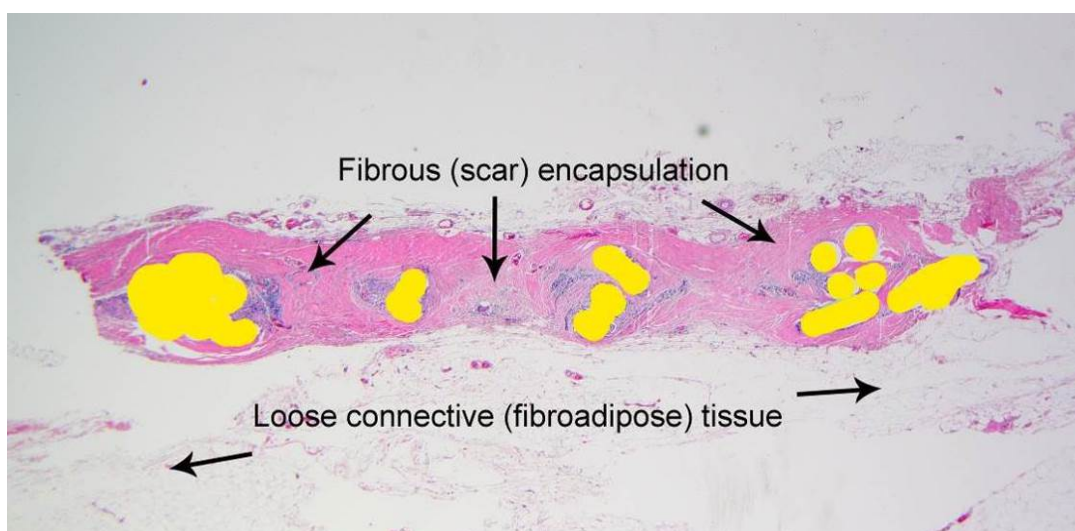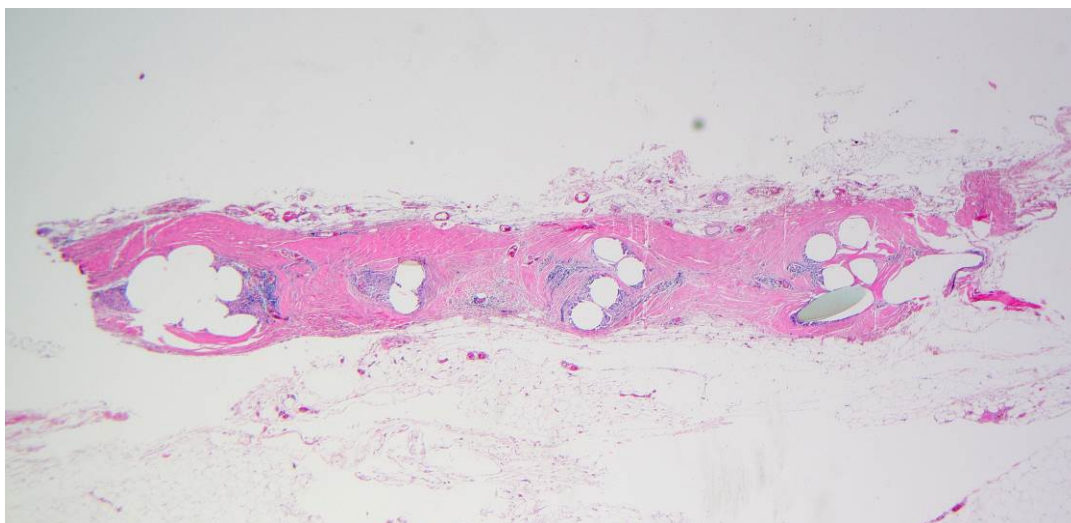
Figure set 2b. Fibrous bridging and scar encapsulation, H&E, 4x.
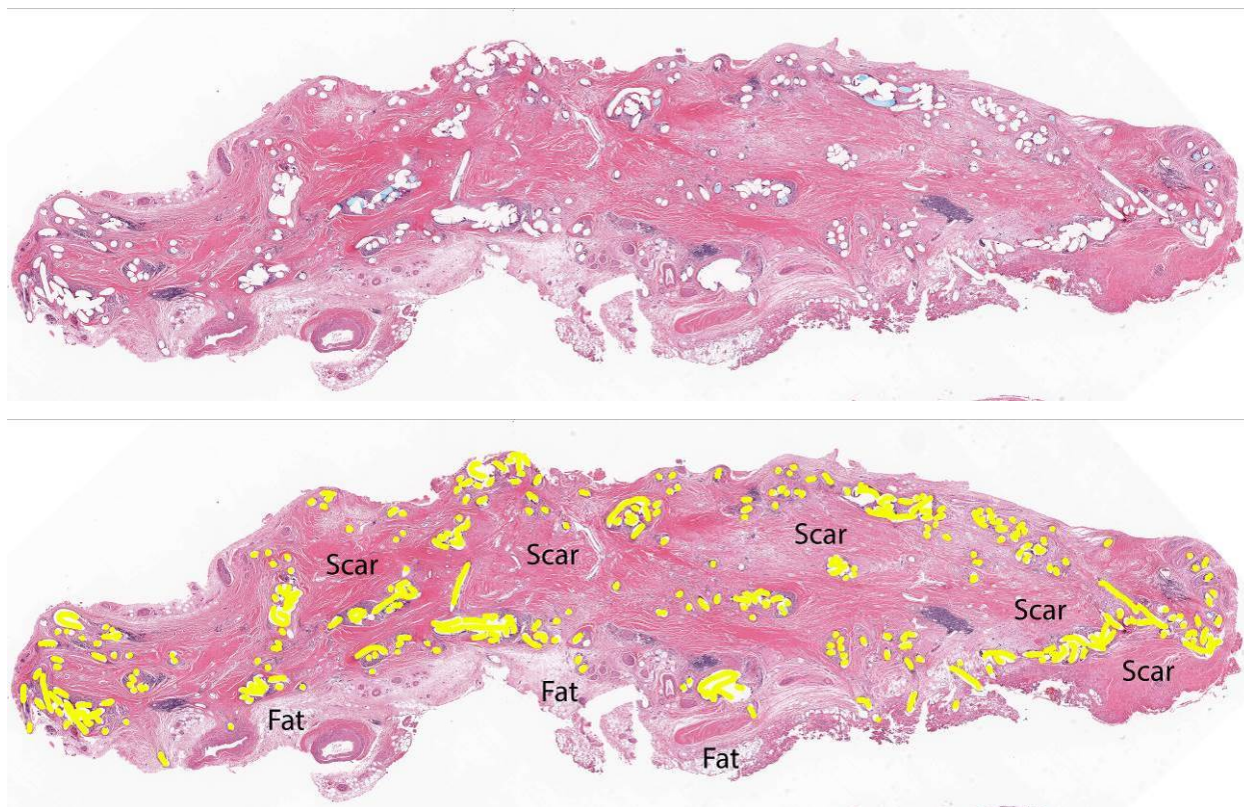
Figure set 2c. Fibrous bridging and scar encapsulation, H&E, 1.6x.

The mesh is incorporated by scar tissue while normal non scarred adipose tissue (fat) is outside of the mesh-scar plate.
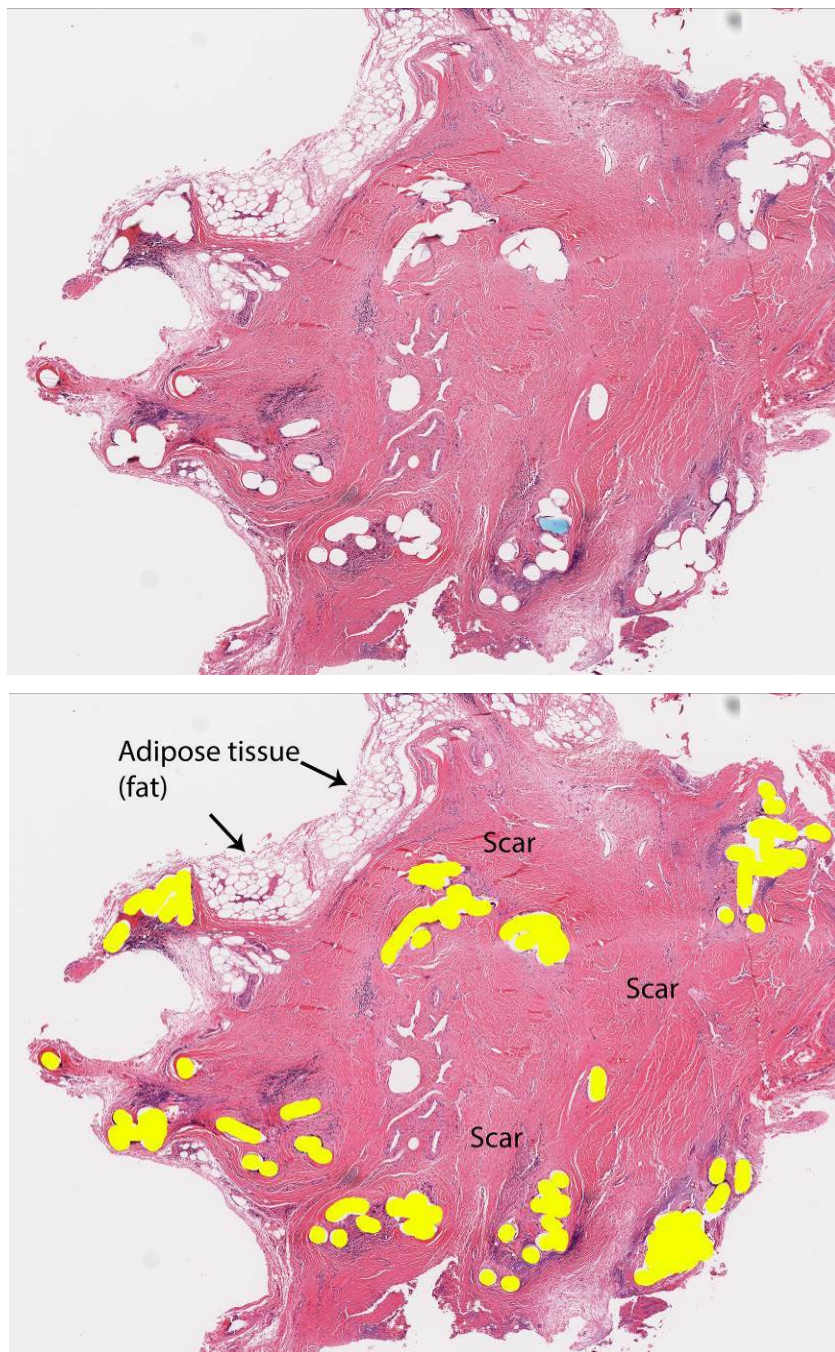
Figure set 2d. Fibrous bridging and scar encapsulation, H&E, 1.6x.

The mesh is incorporated by scar tissue while normal non scarred adipose tissue (fat) is outside
of the mesh-scar plate.
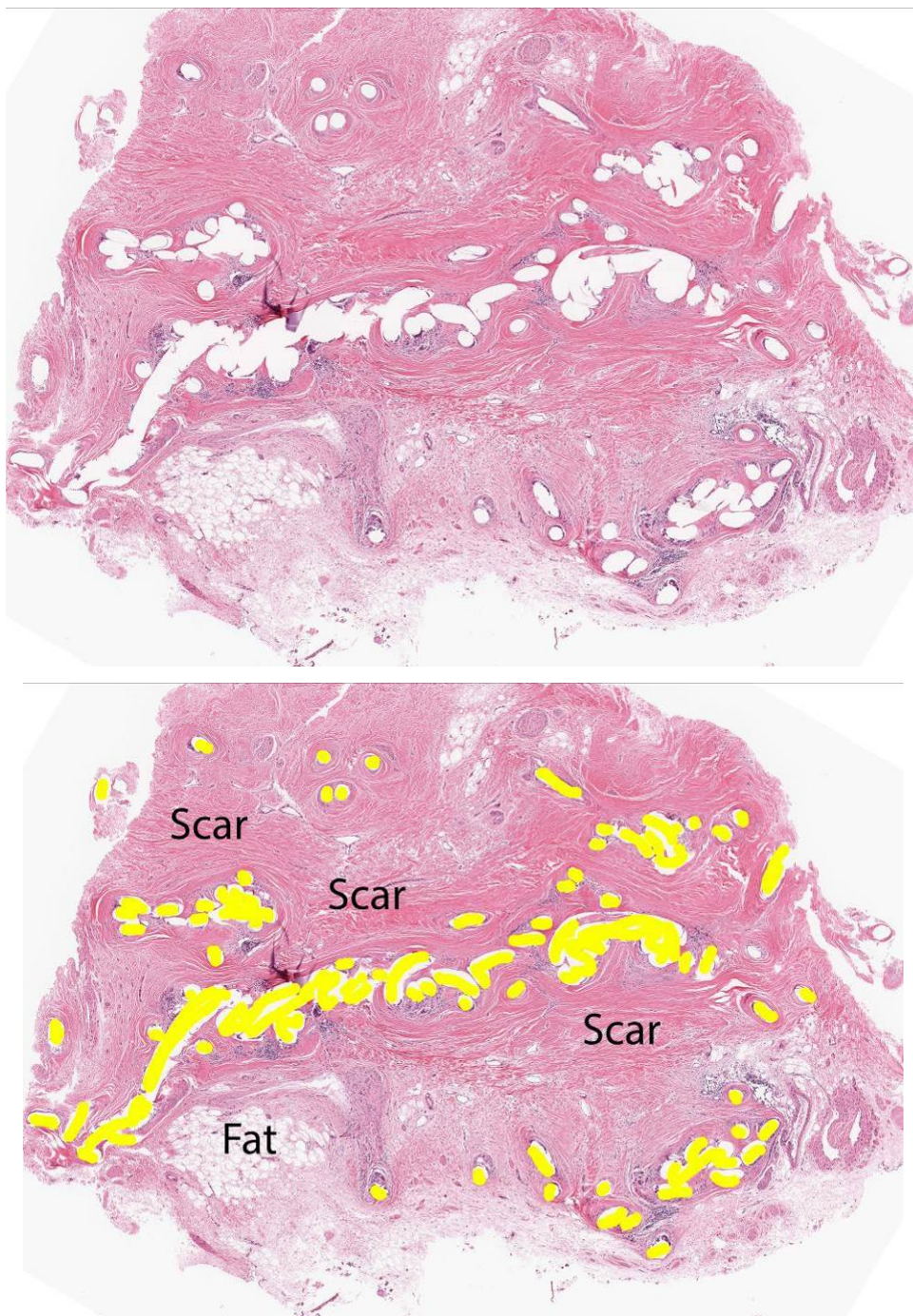
Figure set 2e. Fibrous bridging and scar encapsulation, H&E, 1.6x.

The mesh is incorporated by scar tissue while normal non scarred adipose tissue (fat) is outside

of the mesh-scar plate.
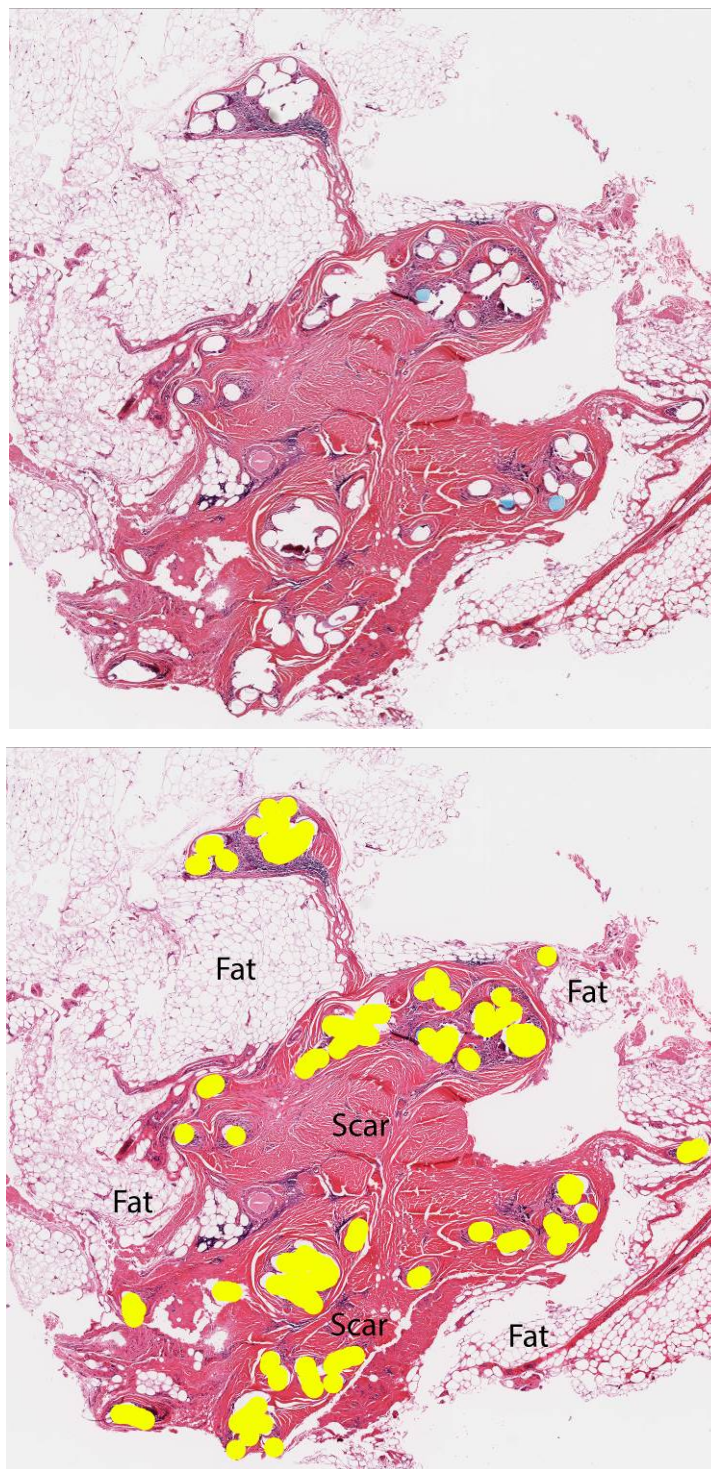
Figure set 2f. Fibrous bridging and scar encapsulation, H&E, 1.6x.

The mesh is incorporated by scar tissue while normal non scarred adipose tissue (fat) is outside of the mesh-scar plate.
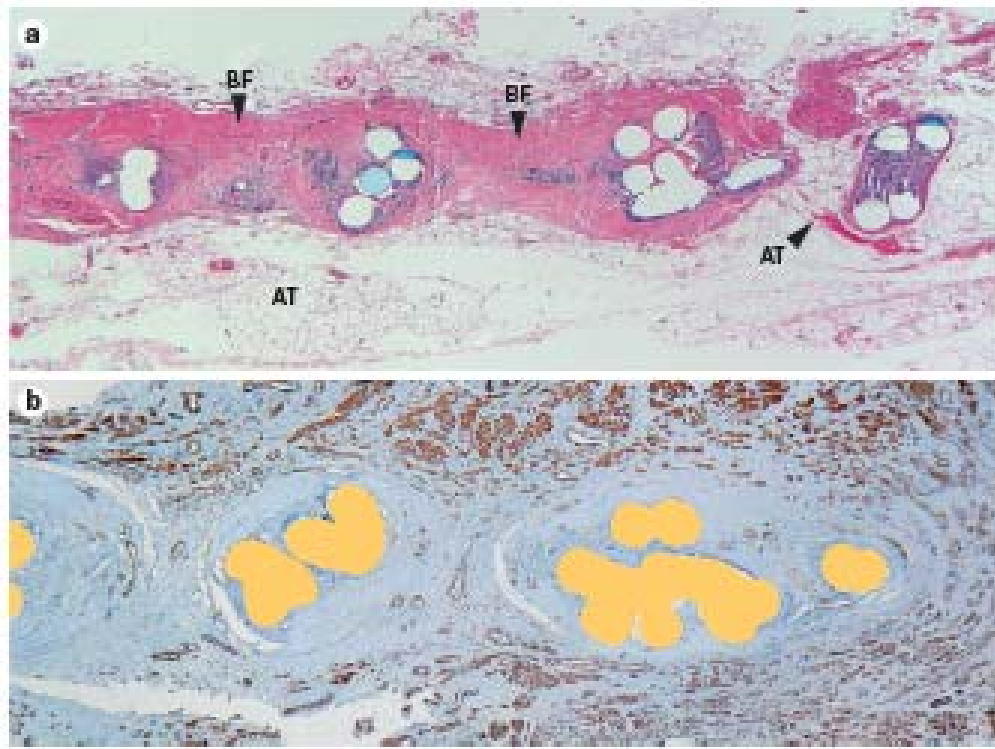
Figure set 2g. Fibrous bridging and scar encapsulation, [557]

"Scar encapsulating mesh and surrounding pre-existent normal adipose and muscular tissues. a | ×2.5 image of a histological section showing a cross-section of mesh filaments as they appear in section, without colouring. Some filaments were labelled blue by the manufacturer. Adipose tissue had been present in the area before mesh placement. Tissue reaction to surgical injury and the mesh generated scar tissue encapsulating the mesh appears as dense pink collagenous tissue. The scar spans, or bridges, across mesh pores, which is termed bridging fibrosis. In this case a terminal pore contains nonscar adipose tissue (arrow with AT). This section has been labelled with a haematoxylin and eosin stain. b | ×2.5 image of a histological section showing cross-sections of mesh filaments. Note that the mesh is surrounded by a halo of fibrous tissue separating it from the pre-existent tissue of the vaginal wall, containing smooth muscle. Smooth muscle is labelled with anti α smooth muscle actin (brown), mesh filaments are filled yellow. The blue colour is a haematoxylin background stain. Abbreviations: AT, adipose tissue; BF, bridging fibrosis".
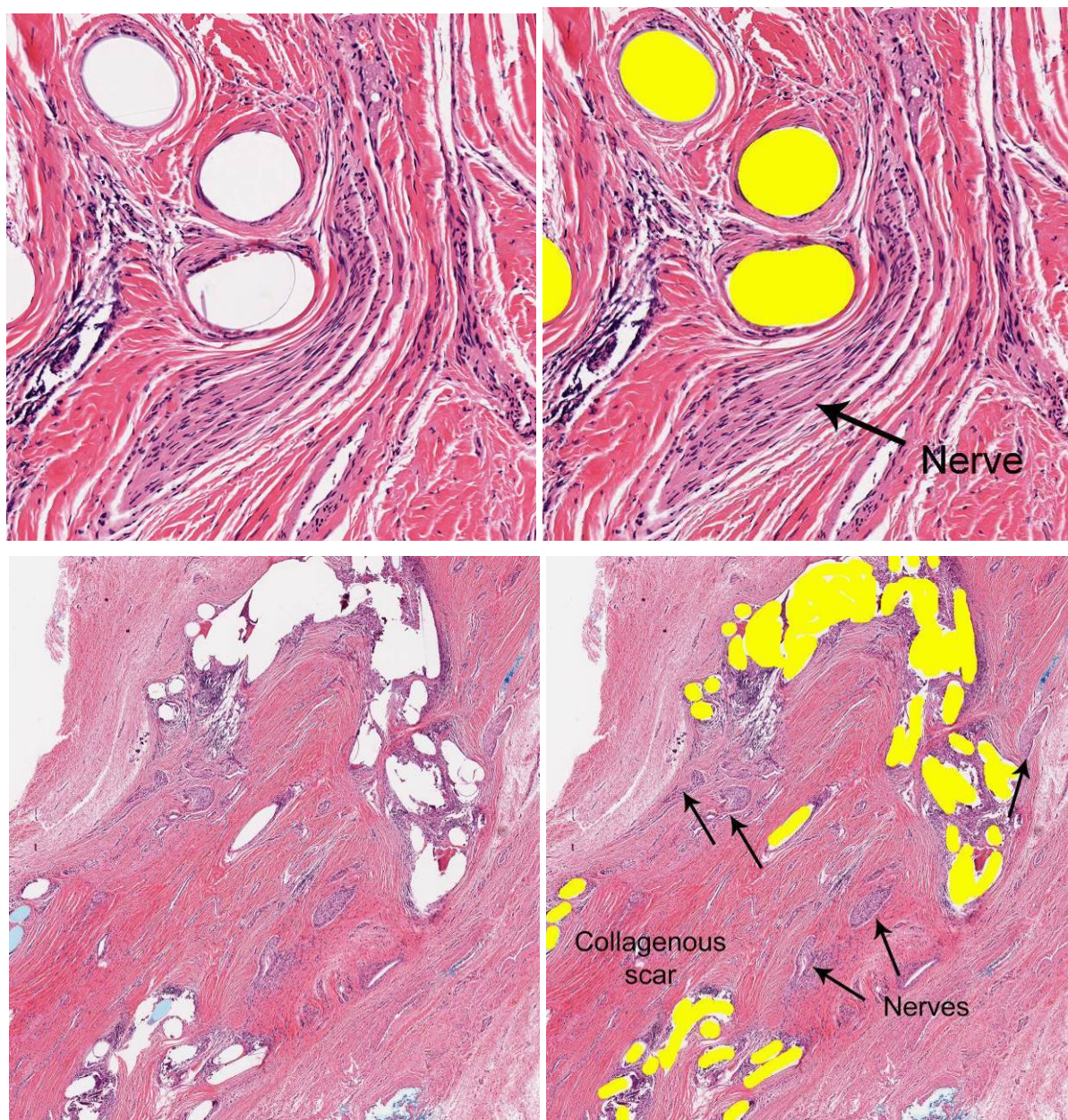
Figure set 3a. Nerves within the mesh spaces (note distortion of the nerve in the upper panel), H&E, 20x and 2.5x.
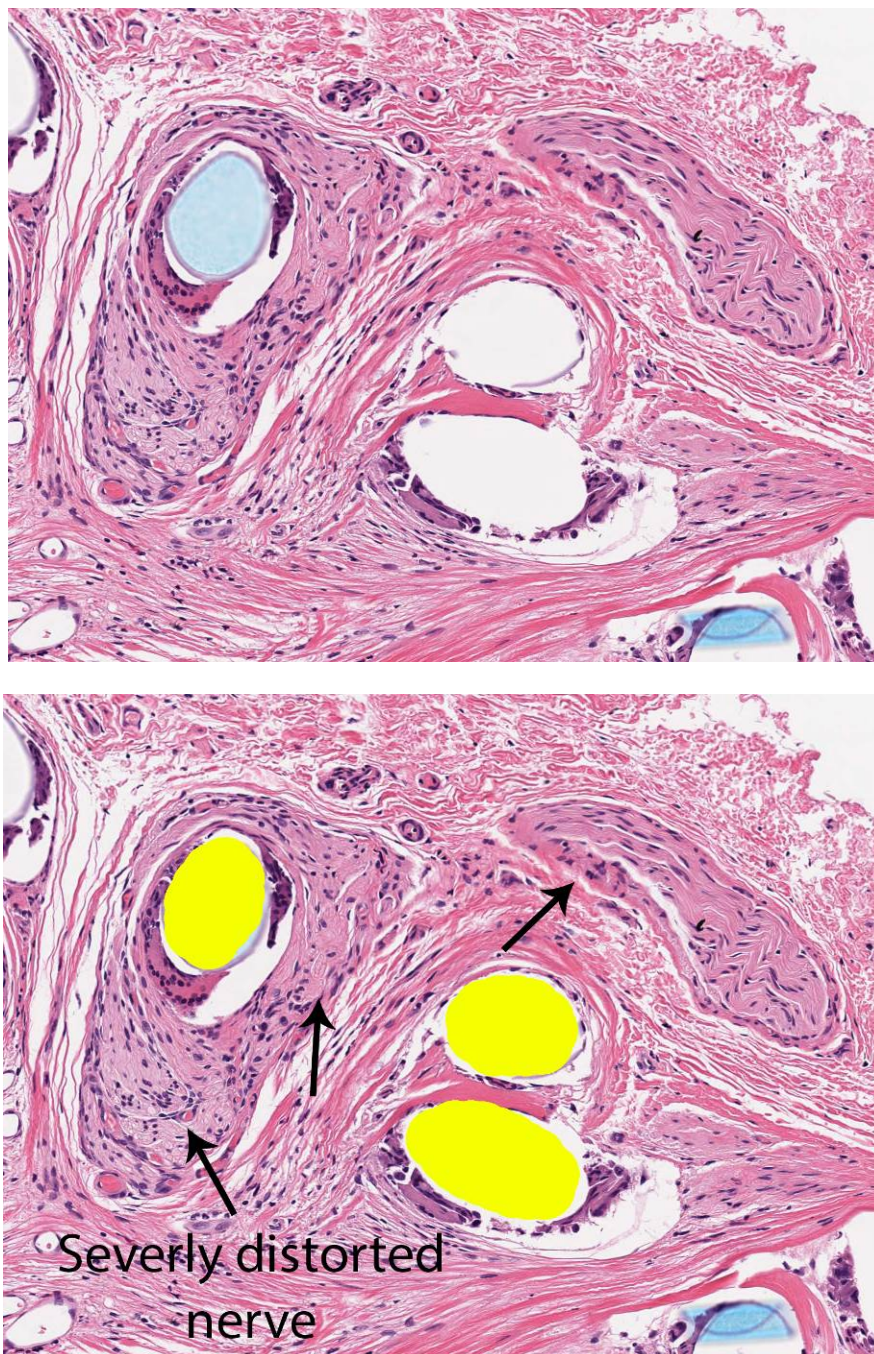
Figure set 3b. Nerves severely distorted by the mesh fibers, H&E, 20x.
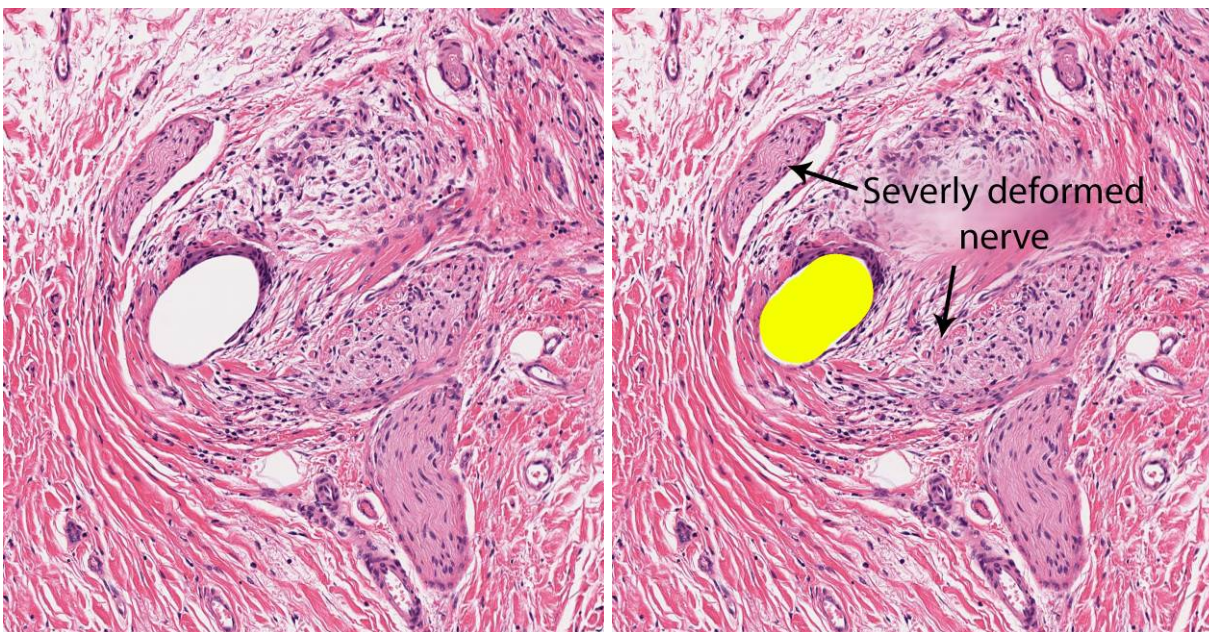
Figure set 3c. Nerves severely distorted by the mesh fibers, H&E, 20x.
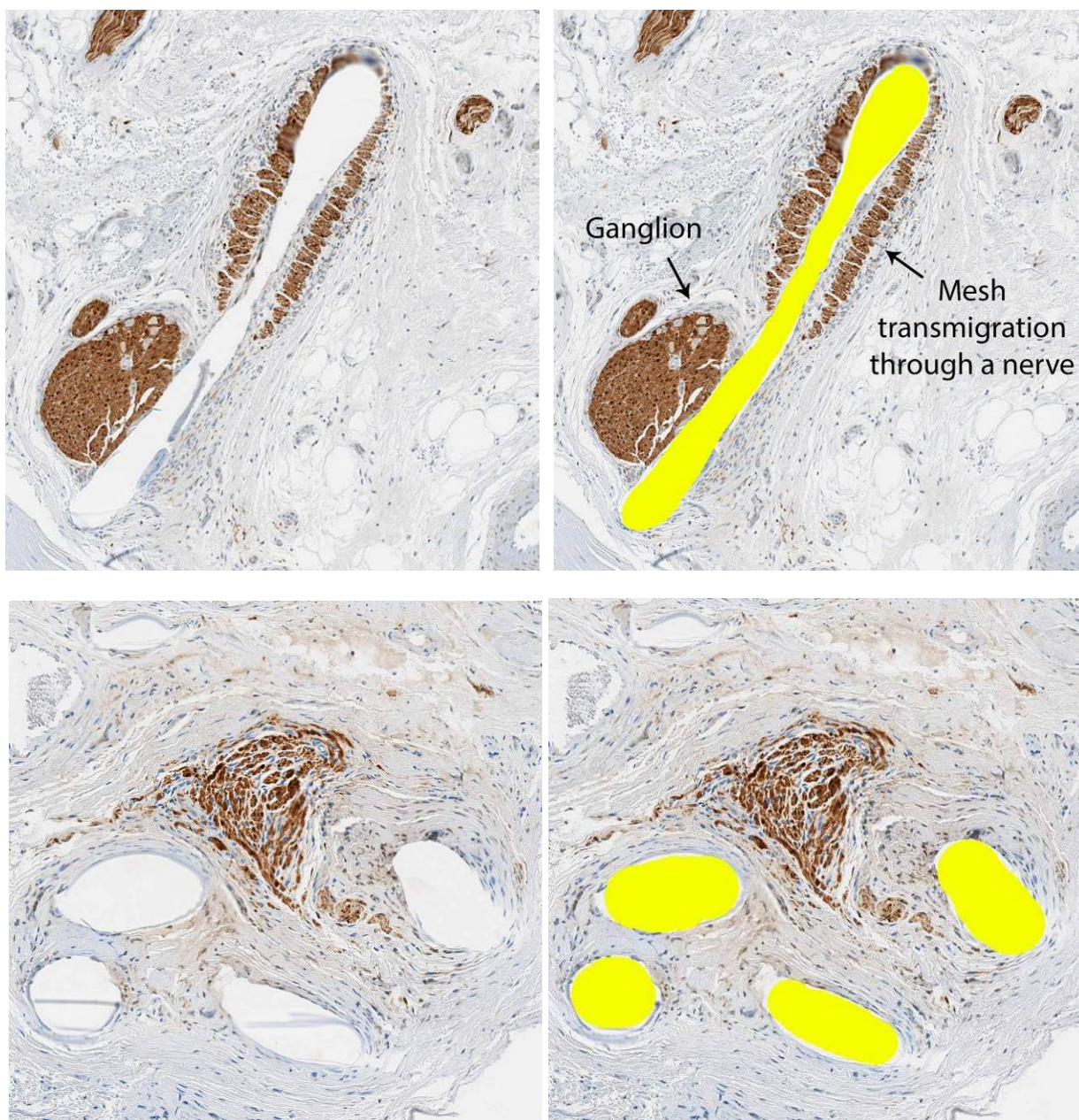
Figure set 3d. Nerves severely damaged by the mesh fibers, H&E, 20x.

The nerve in the upper panel is nearly transected longitudinally. The nerve in the lower panel has separation of the fascicles in the scar tissue = traumatic neuroma.

34
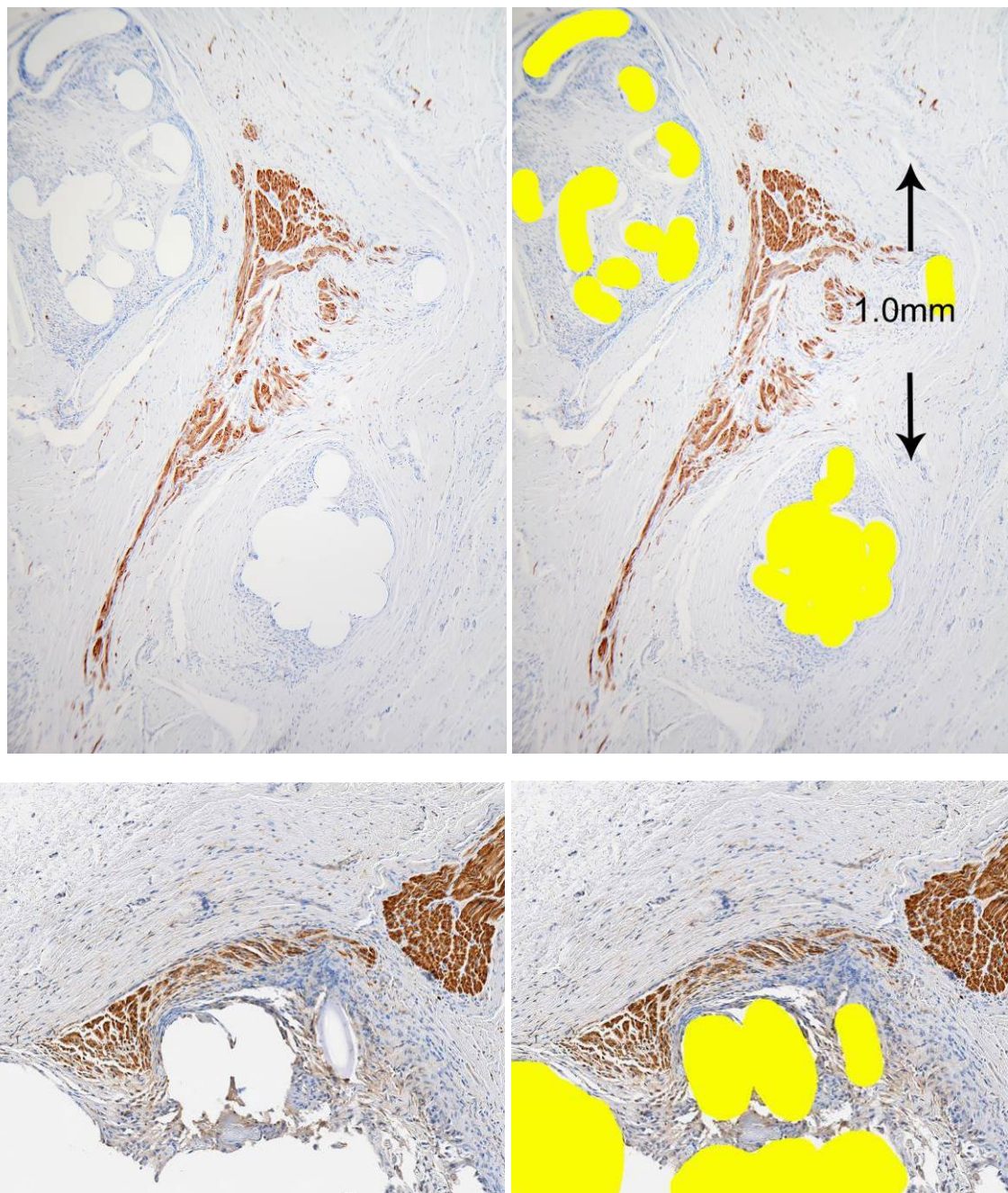
Figure set 3e. Deformation of the nerves and formation of traumatic neuromata, S100, 4x and 10x.
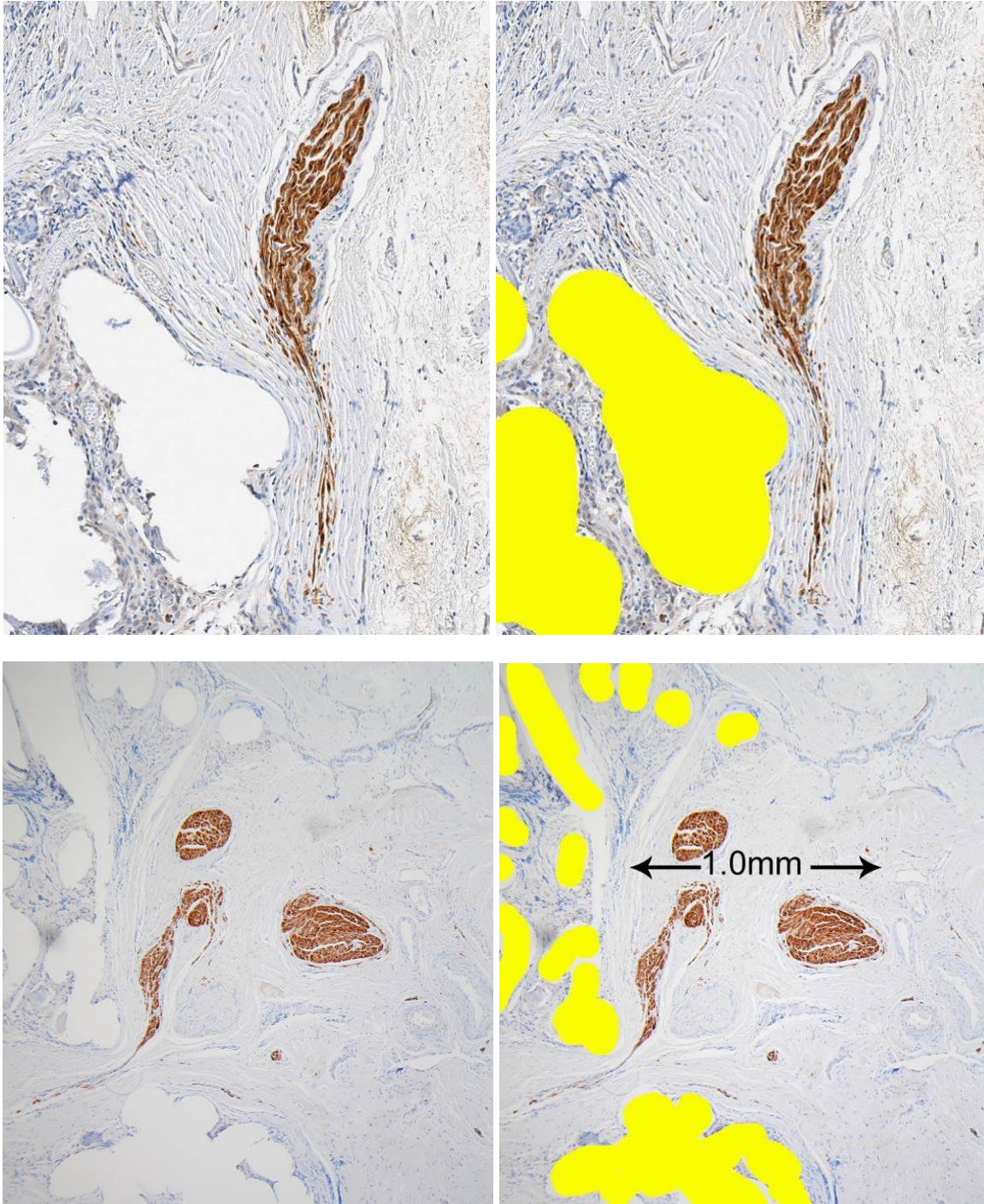
Figure set 3f. Deformation of the nerves, S100, 20x and 10x.
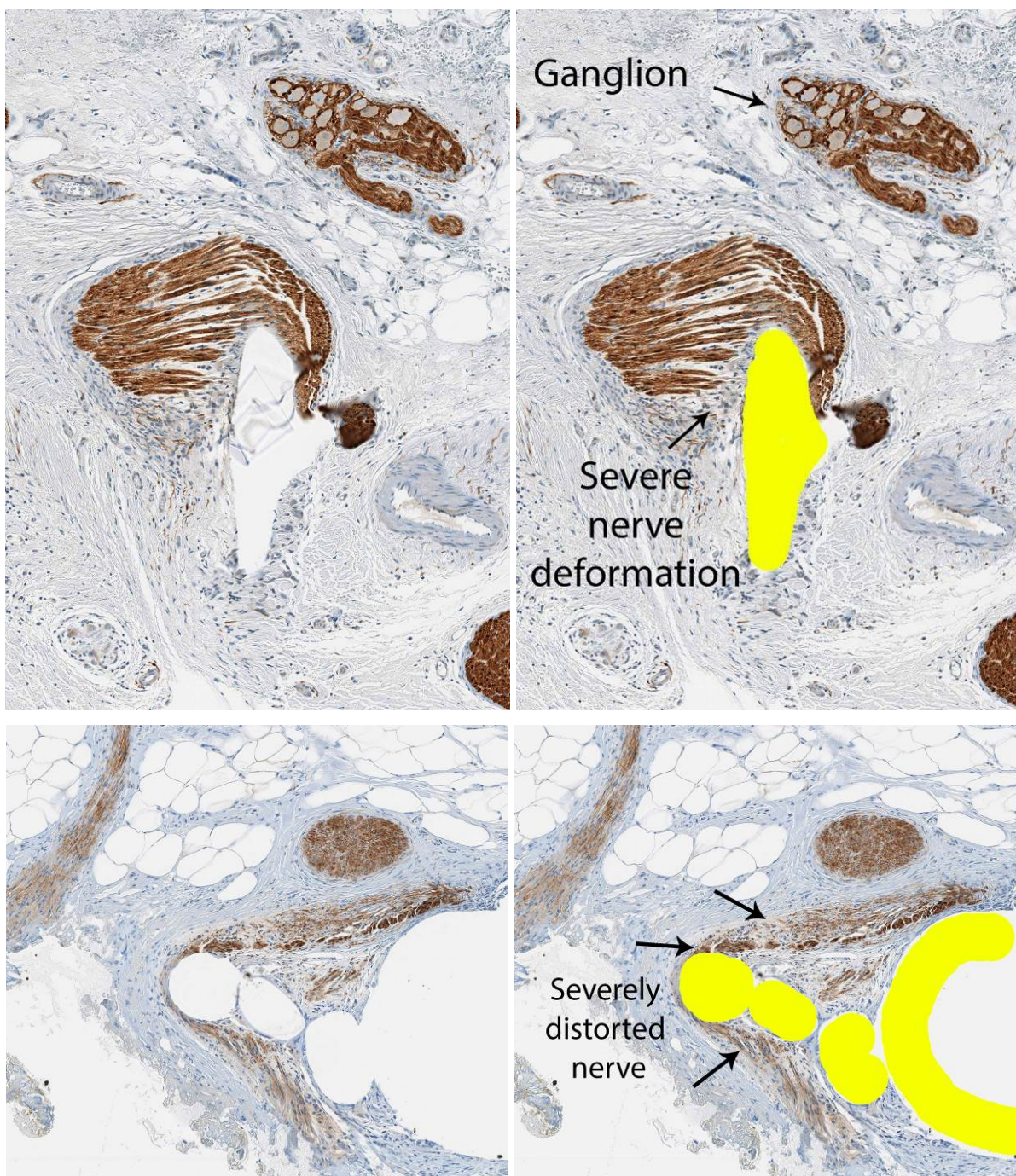
Figure set 3g. Severe deformation of the nerves by the mesh fibers, S100, 20x.

The nerve in the lower panel has separation of the fascicles as occurs in tramatic neuromata.
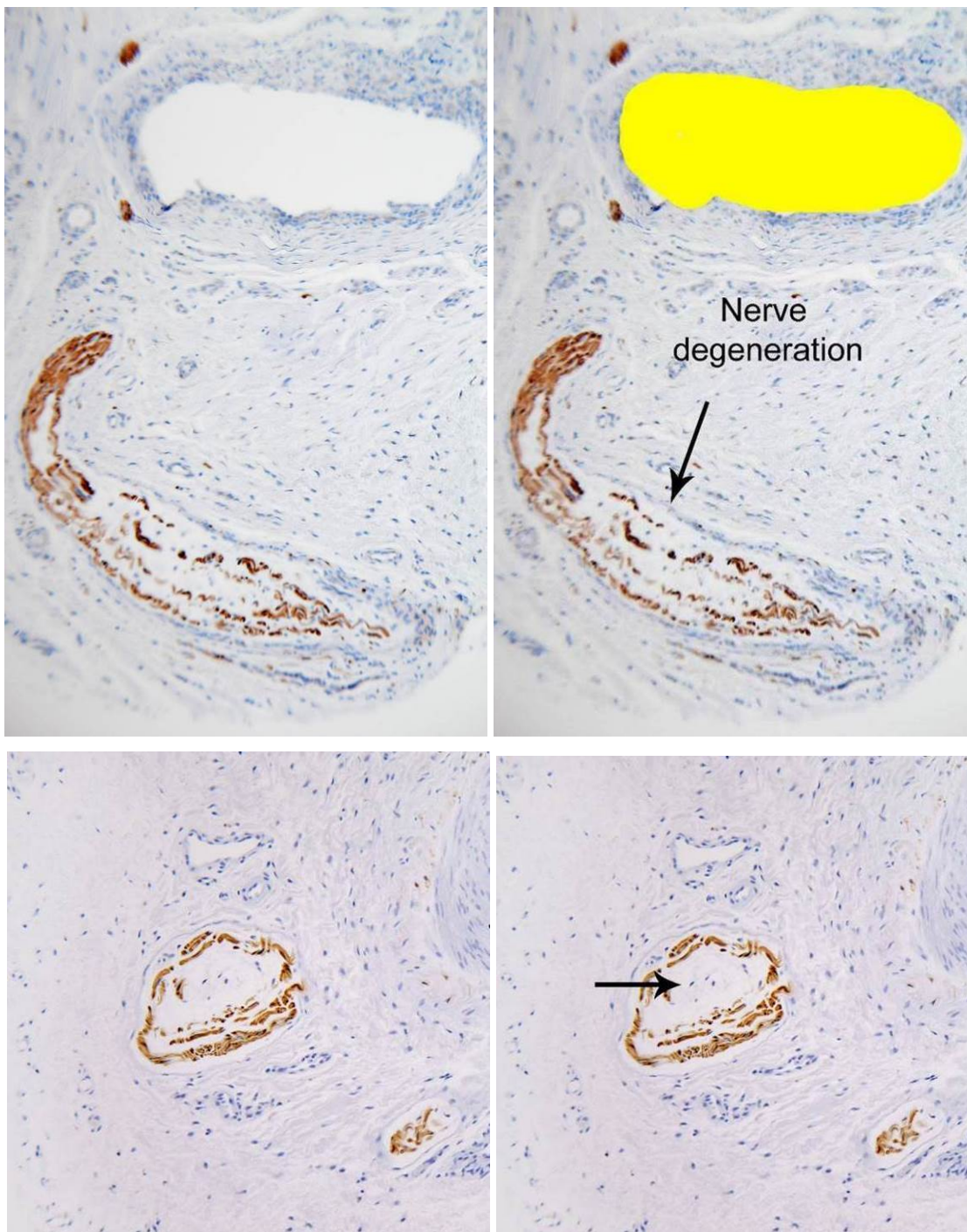
Figure set 3h.Degeneration of affected nerves, s100, 20x,

Degenerative type of changes in peripheral nerves, Renaut bodies have been associated with

cronic nerve trauma and entrapment [567-570].
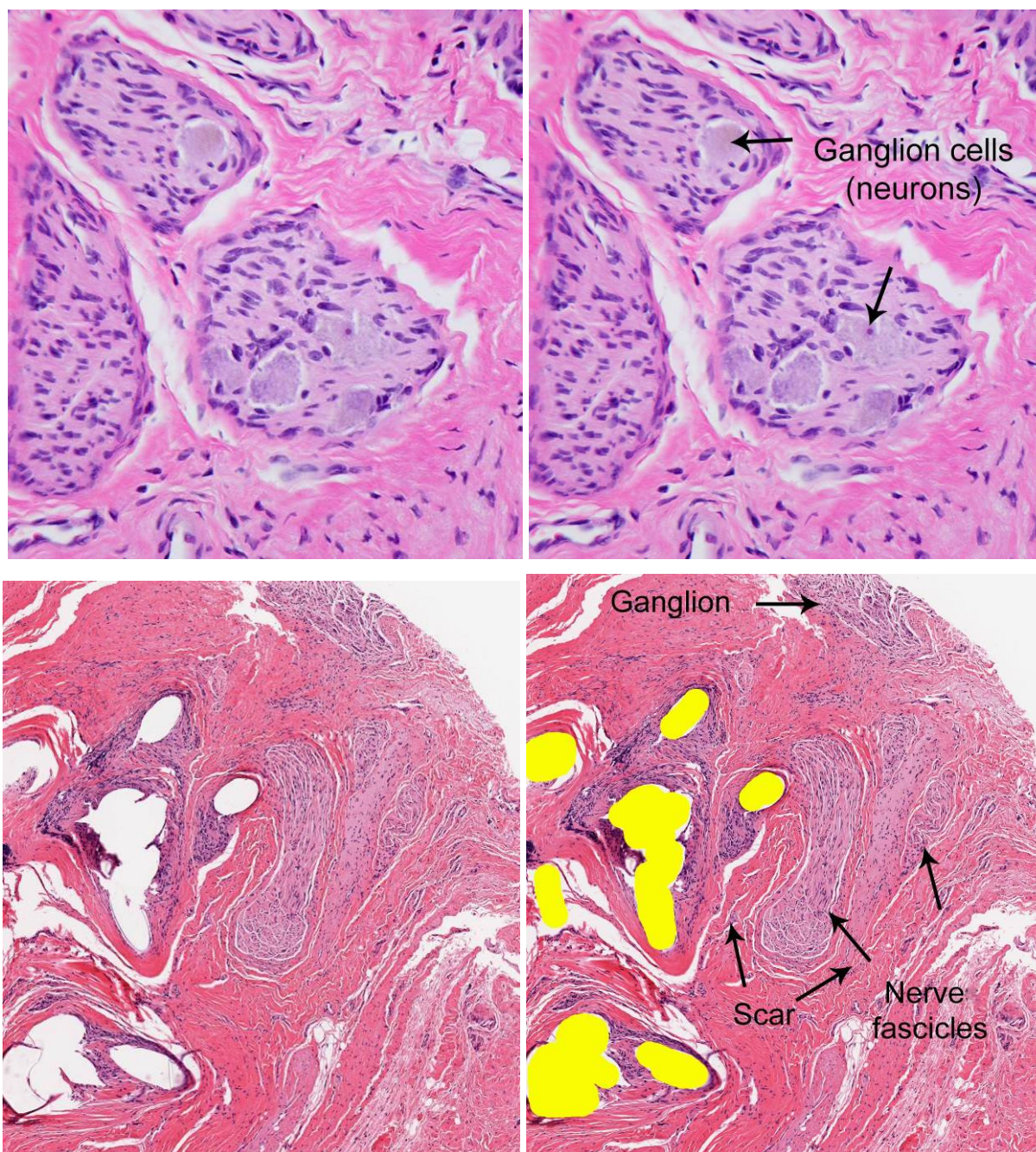
Figure set 4a. Neural ganglia, H&E, 40x and 4x.
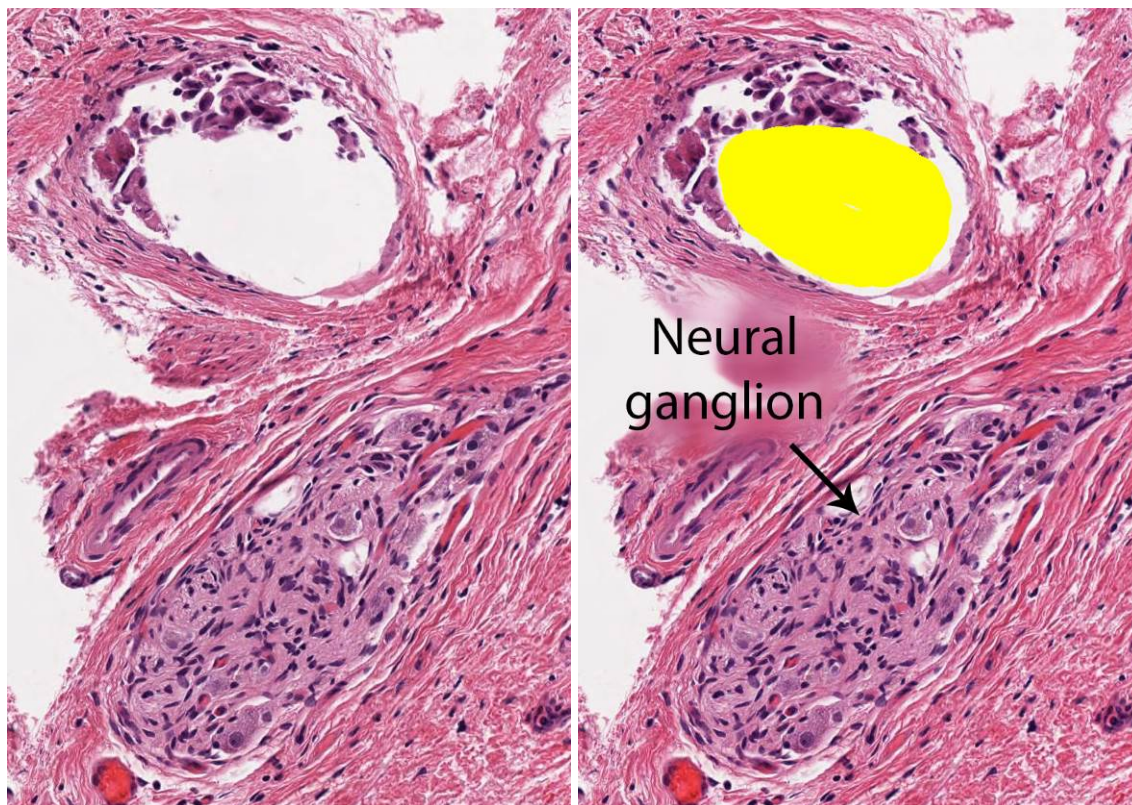
Figure set 4b. Neural ganglion affected by the mesh, H&E, 20x.
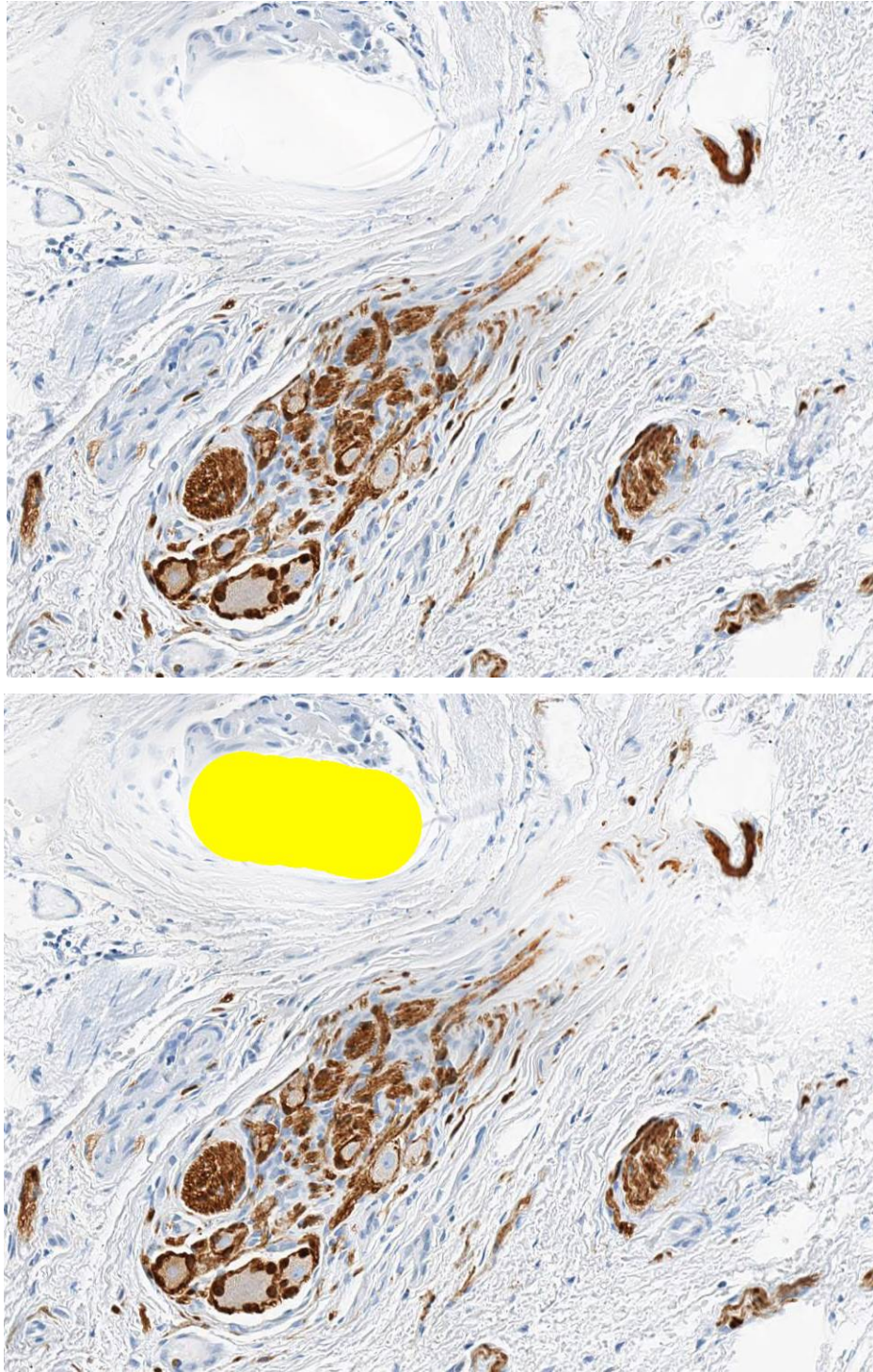
Figure set 4c. Neural ganglion affected by the mesh, H&E, 20x.
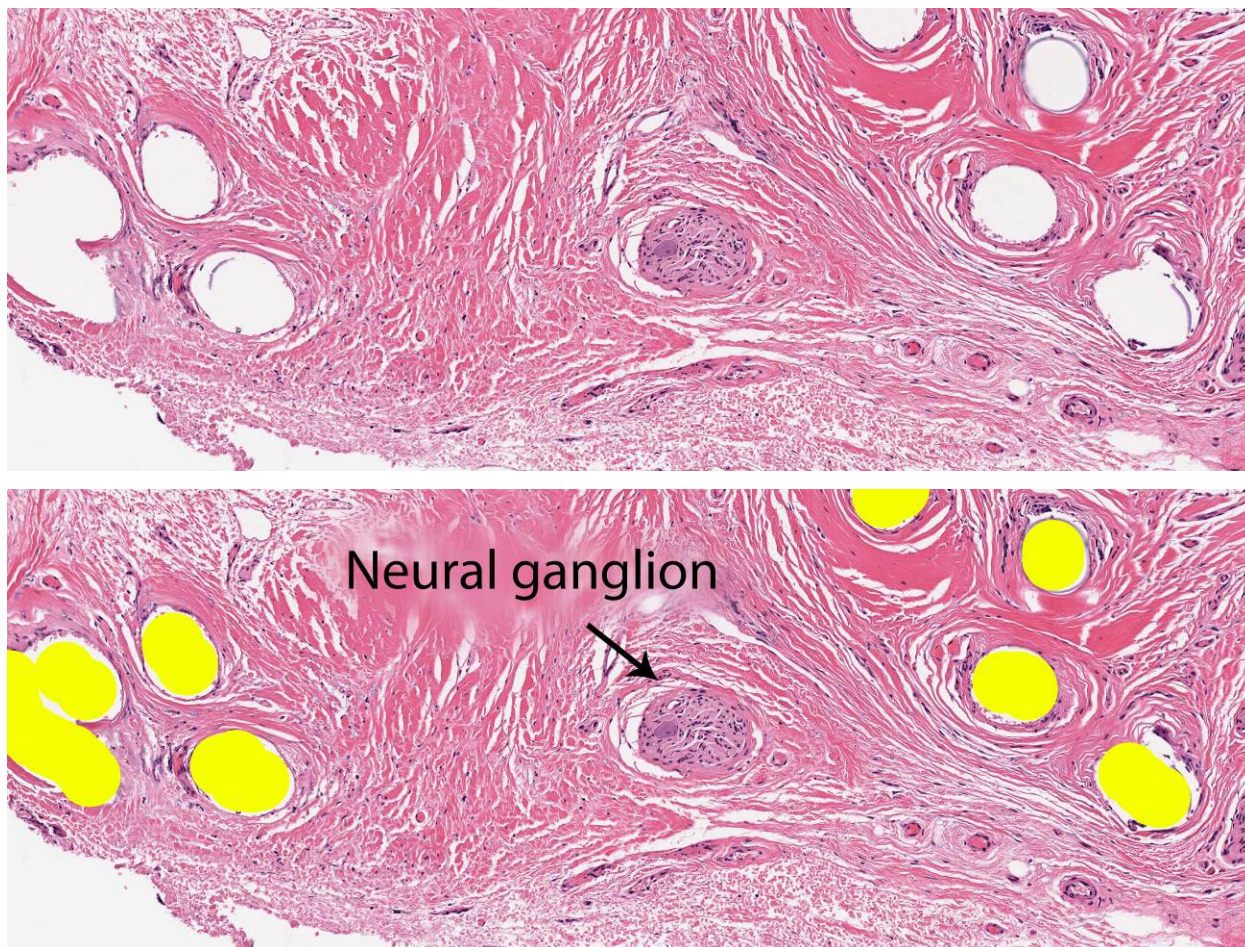
Figure set 4d. Neural ganglion affected by the mesh, H&E, 20x.
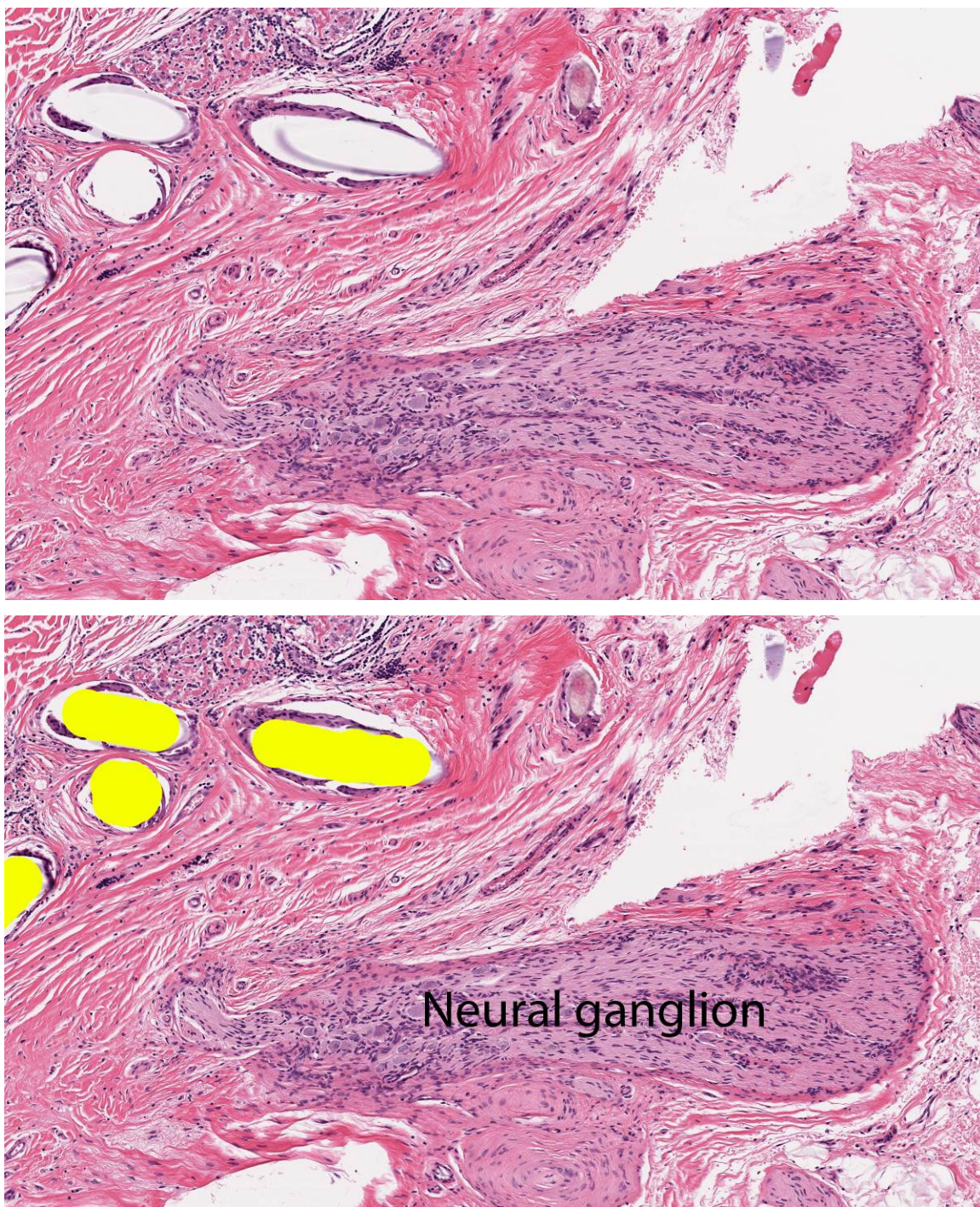
Figure set 4e. Neural ganglion affected by the mesh, H&E, 20x.
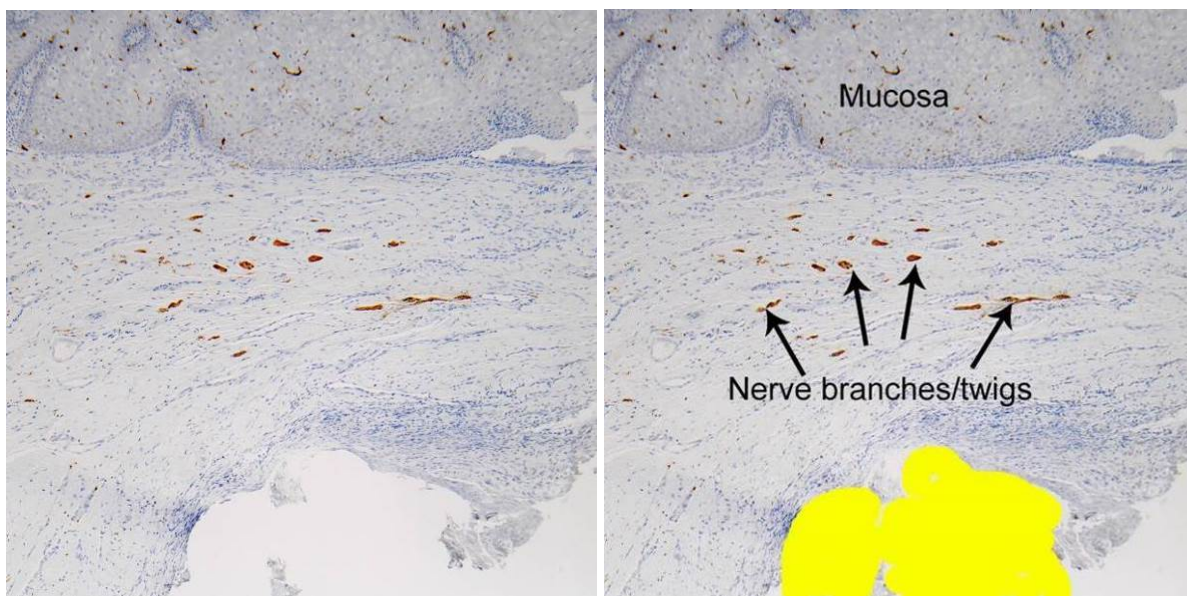
Figure set 5.Innervation of mucosa overlying the mesh, s100, 4x.
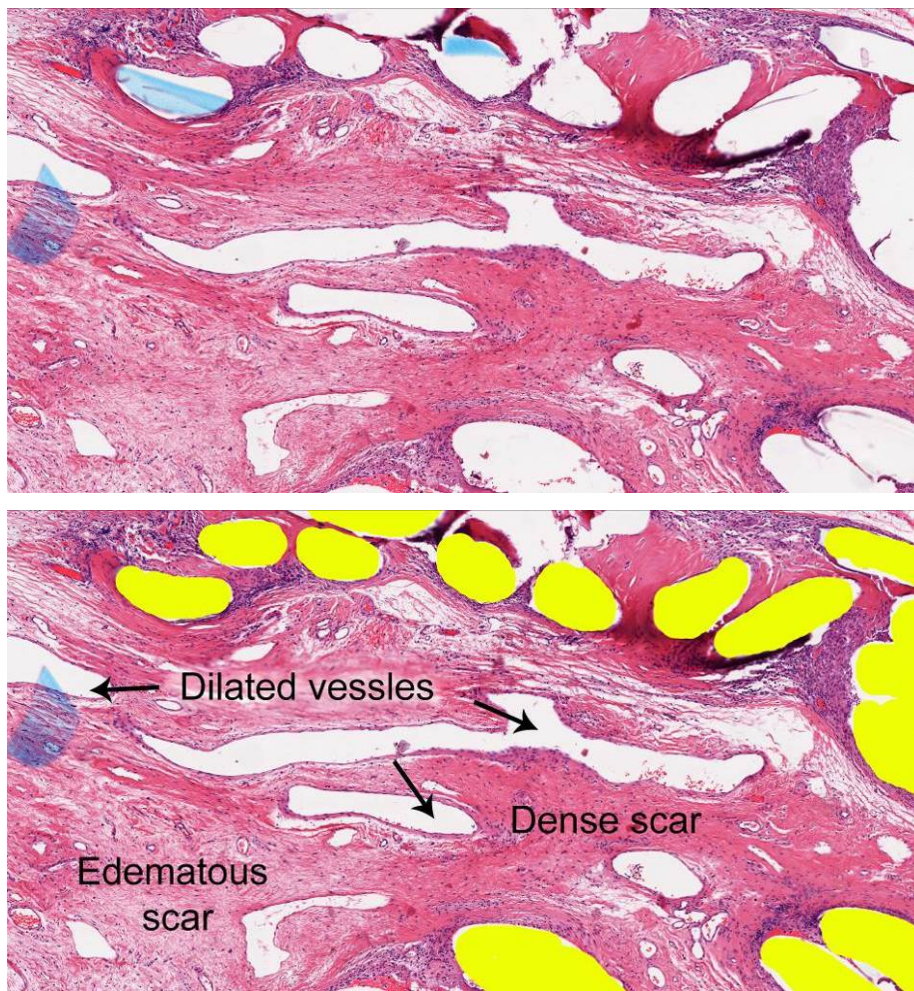
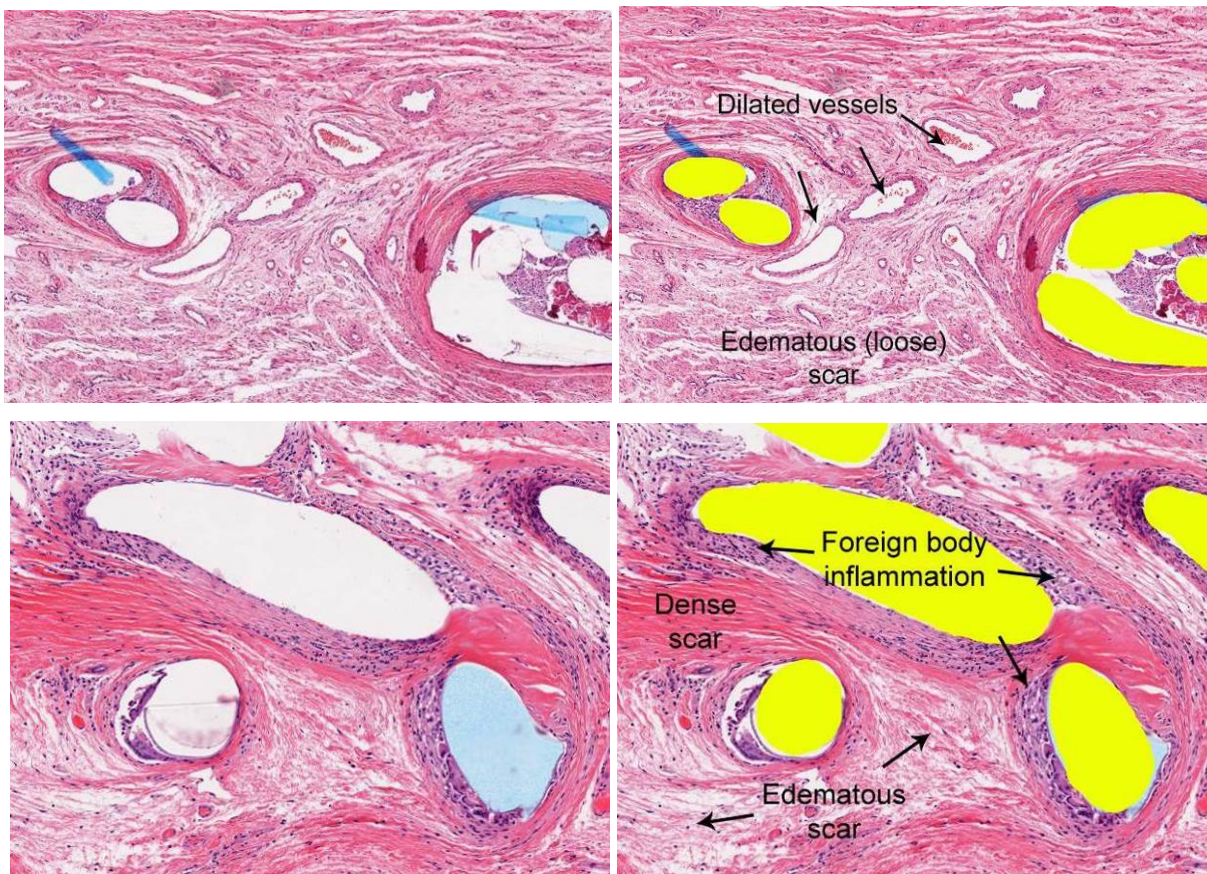Figure set 6a.Vascular dilatation and tissue edema, H&E, 4x.

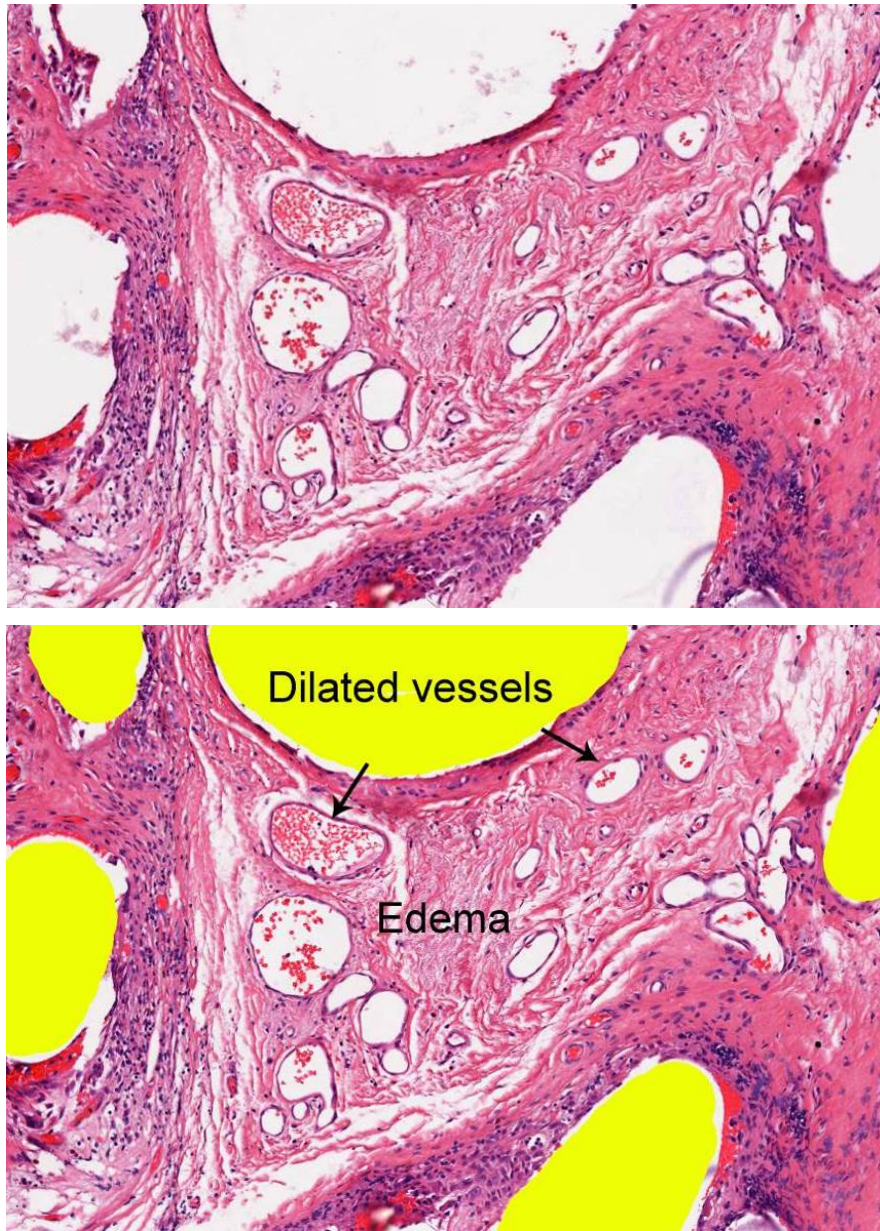Figure set 6b.Vascular dilatation and tissue edema, H&E, 4x and 10x.

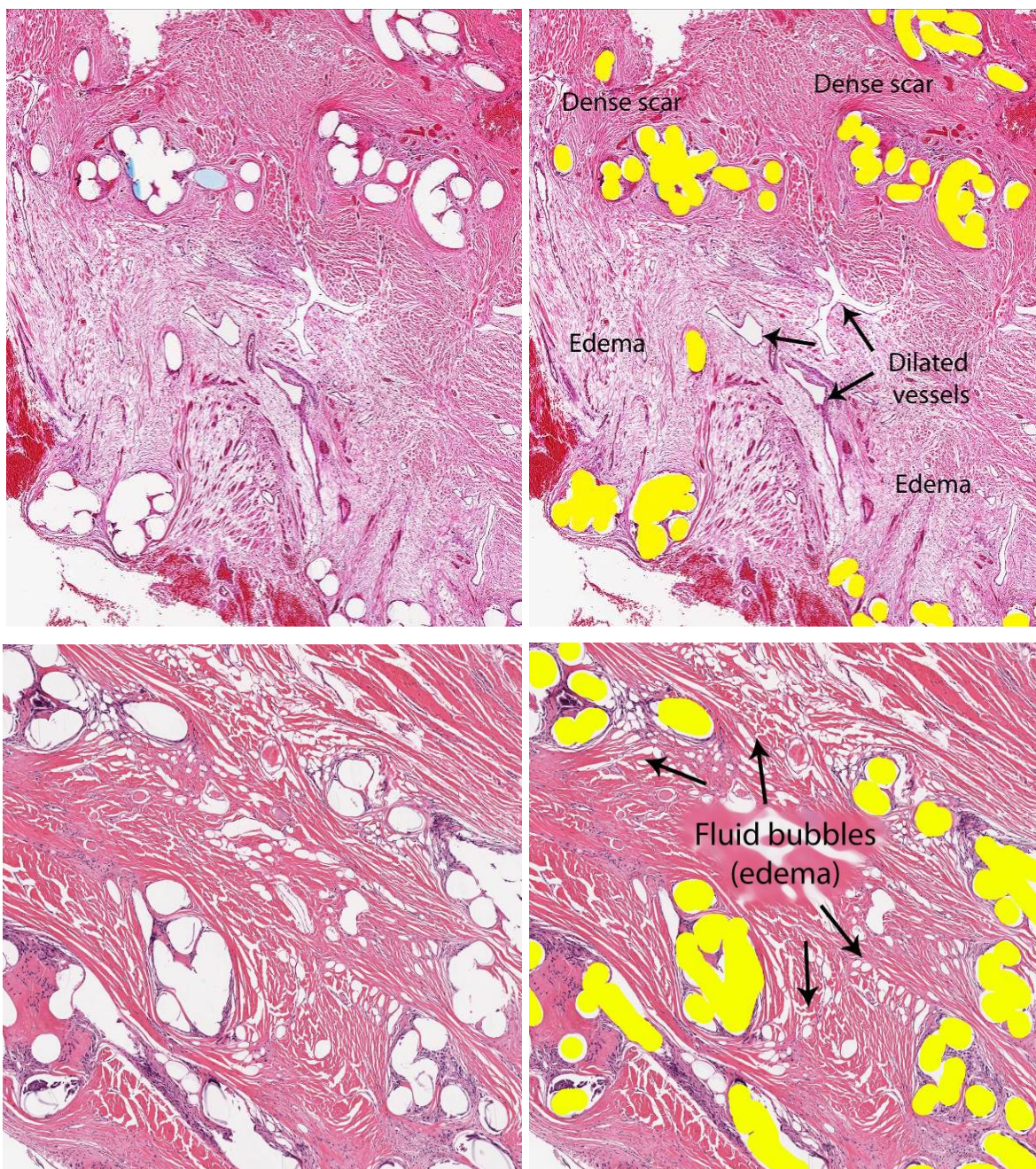Figure set 6c. Vascular dilatation and tissue edema, H&E, 10x.

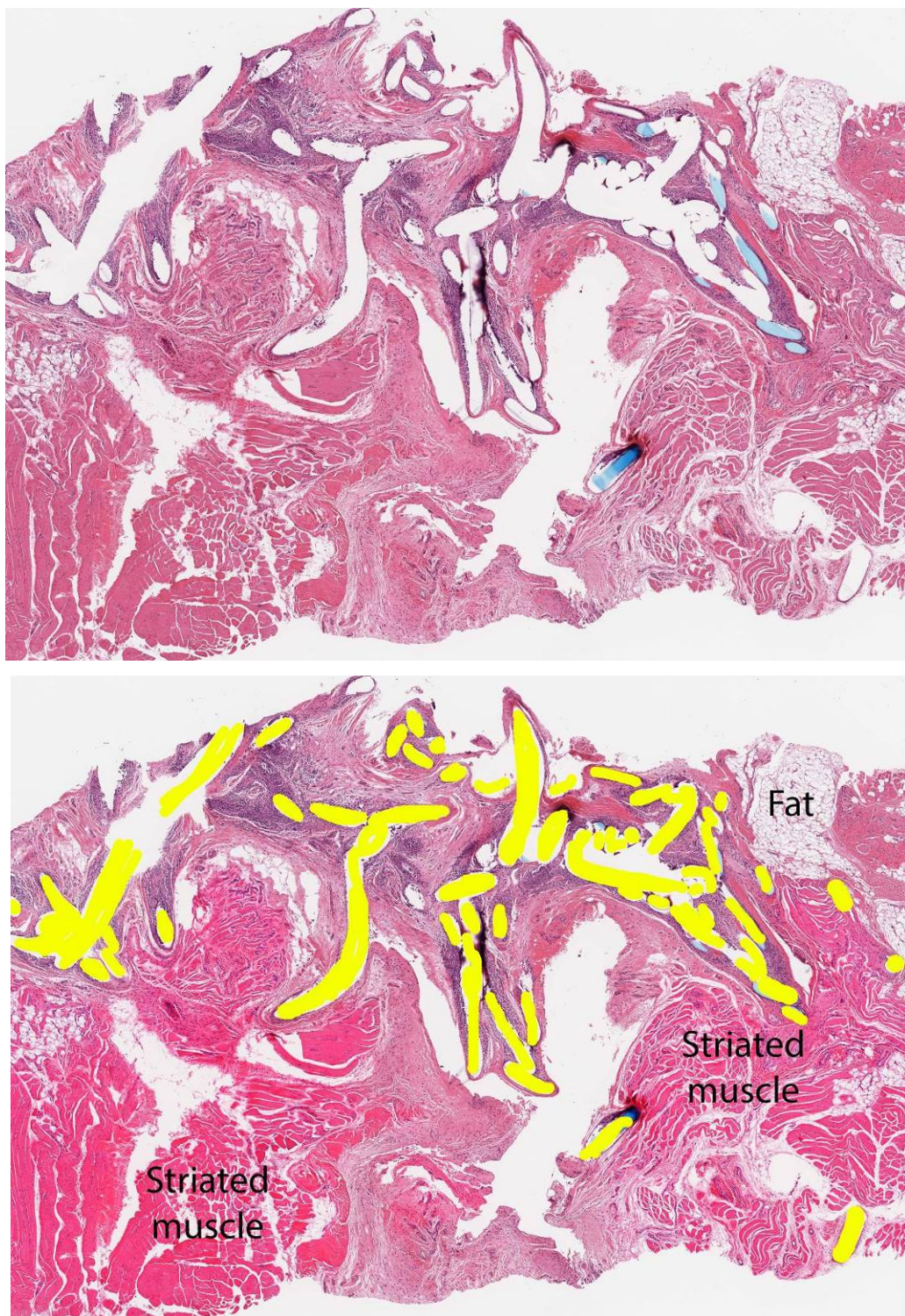Figure set 6d. Vascular dilatation and tissue edema, H&E, 4x.

Figure set 7a.Involvement of striated muscle by the mesh, H&E, 1.6x